

**HEALTH EFFECTS OF
EXPOSURE TO
ENVIRONMENTAL TOBACCO SMOKE**

**APPENDIX B
SUMMARY OF PUBLIC COMMENTS
AND RESPONSES ON
THE FEBRUARY 1997 FINAL DRAFT**

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Table of Contents

List of Those Commenting	B-ii
General Remarks, Executive Summary and Introduction	B-1
Exposure Measurements and Prevalence	B-29
Developmental Toxicity and Reproductive Effects.....	B-42
Respiratory Health Effects	B-69
Carcinogenic Effects	B-107
Lung Cancer	B-107
Cancers Other than Lung Cancer	B-156
Cardiovascular Health Effects.....	B-169

List of Those Commenting

Philip Morris

Philip Morris USA, submitted by Richard Carchman, Group Director
Scientific Affairs

Stuart Brody, University of Tübingen

Nigel A. Brown

Dennis A. Frate

Michael Glovsky, Huntington Hospital

Lawrence B. Gratt & Willard R. Chappell, IWG Corp (Gratt), University of
Colorado at Denver (Chappell)

Bruce Kelman, Golder Associates

Daniel Lackland

Zadok Ruben, Patoximed Consultants

Thomas B. Starr, ENVIRON International Corp

David Sylwester, University of Tennessee

R.L. Tweedie & M.J. Merilees, Colorado State University (Tweedie), University of
Auckland (Merilees)

The Tobacco Institute

The Tobacco Institute, submitted by Clausen Ely, attorney for the Tobacco
Institute

Gio Batta Gori, The Health Policy Center

Maurice E. LeVois & Maxwell W. Layard, Environmental Health Resources

Raphael J. Witorsch, Virginia Commonwealth University

RJ Reynolds

RJ Reynolds, submitted by Mary Ward, attorney for RJ Reynolds

William J. Butler, Environmental Risk Analysis

ChemRisk, submitted by Richard J. Wenning

Others

Michael P. Eriksen, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion

Gordon L. Fung, American Heart Association

Stanley M. Greenfield

Robin Hobart, Americans for Nonsmokers' Rights

Donald O. Lyman, Department of Health Services, Division of Chronic Disease and Injury Control

Otto J. Mueksch

Wayne R. Ott, Stanford University, member Cal-EPA Science Advisory Board

James L. Repace

Marty Ronhovdee

Claudia Rosa-Beinenfeld

Louis Rosenberg

John Slade, American Society of Addiction Medicine

Jay R. Schrand

Linda Stewart

Carol Thompson, Smokers' Rights Action Group

Judson Wells

Comment Summaries and Responses for General Remarks, the Executive Summary and the Introduction (Chapter 1)

Philip Morris

Philip Morris, USA, submitted by Richard Carchman, attorney for Philip Morris

1. Comment Summary: “The final draft does not meet the RAAC [Risk Assessment Advisory Committee of the OEHHA Science Advisory Board] recommendation that Cal/EPA seek early input into the risk assessment process”. “The final draft does not meet the RAAC recommendation that Cal/EPA provide a forum for the identification ... of new or existing knowledge which can improve the scientific basis for risk assessment in California.” The conduct of public workshops and response to comments are criticized.

Response: The process has included multiple opportunities for input from members of the public. OEHHA and ARB sponsored a workshop in October 1992 to obtain public input early in the evaluation of ETS health effects and exposure in California. At the workshop, preliminary thoughts on the direction of the ETS assessment were discussed with participants, which included individuals from local, state and federal government agencies, universities and other research organizations, representatives of the tobacco industry, and public interest groups.

Public release and review on each major area of health effects occurred as they were prepared. The first two documents (*Respiratory Health Effects of ETS* [current Chapter 6] and *The Role of ETS in Cancers Other Than Lung Cancer* [sections in Chapter 7]) were mailed in May 1994 to those on the ETS mailing list (and all others requesting copies), and a public workshop held on the documents during the public comment period. Subsequent documents were released in September 1994 (*Cardiovascular Health Effects of Exposure to ETS* [current Chapter 8]), March 1995 (*Developmental and Reproductive Effects of Exposure to ETS* [current Chapters 3, 4, 5]), September 1995 (*ETS: Exposure Measurements and Prevalence* [current Chapter 2]), and January 1996 (*Carcinogenic Effects of Exposure to ETS, Excerpt: ETS and Lung Cancer* [now a section in Chapter 7]). For each release, OEHHA received public comment, and during the comment period held a workshop. Following a public comment period, each document was revised to respond to comments received and updated to include critical new studies; these revised documents have been compiled to form the current assessment. The document *Developmental and Reproductive Effects of Exposure to ETS* underwent additional review, in May 1995, as a hazard identification document by the eight member Developmental and Reproductive Toxicant Identification Committee of the OEHHA Scientific Advisory Board.

The *Final Draft for Scientific, Public, and SRP Review*, which was comprised of the documents named above as well as an Introduction and Executive Summary, was released

for additional public review and comment. It was made available on the OEHHA website in late February 1997, and announced in the *California Regulatory Notice Register* and sent to all those on the mailing list in early March 1997. A public forum to provide the opportunity for verbal public comment was also held during the public comment period, which closed on May 5. The public forum was not a public workshop, and all authors of the document were not present. Authors on the various sections of the document presented and were available to respond to public comment at the 8 public workshops and meetings that were held on the major areas of health effects covered.

The purpose of the document is to provide an evaluation of possible ETS health effects. Public meetings and comment periods have been provided to accommodate input specifically directed to ETS risk assessment. OEHHA has noted and responded to those comments and submissions which add materially to the discussion of ETS health effects, but cannot comment exhaustively on every item submitted. Numerous changes have been made to the ETS report in response to public input received during the course of its development.

Philip Morris raised Chapter 2 in the *Final Draft* as a special example of OEHHA not being responsive to comments it submitted. Comments received by Philip Morris and others suggested that the chapter was being mistaken for a comprehensive exposure assessment. Various wording changes were made to clarify the scope of that chapter, which was developed primarily to provide background for the remainder of the ETS report on investigation and monitoring methods used in epidemiological evaluations and to provide information on ETS prevalence. OEHHA reviewed the papers submitted by Philip Morris and has added some of them to Chapter 2; other papers that are not included either do not present new information or are only marginally related to the issue being discussed.

OEHHA regrets that responses to a few of the submissions received on the lung cancer excerpt released in January 1996 were inadvertently omitted from Appendix A. Responses to comments submitted on the lung cancer except by Philip Morris USA and the RJ Reynolds Tobacco Company were not included in Appendix A while responses to submissions by scientists on behalf of these institutions were. Appendices A and B now provide responses to the major scientific issues raised on the lung cancer section during the public comment periods by Philip Morris and the RJ Reynolds Tobacco Company, as well as by the others commenting.

2. Comment Summary: “The final draft omits consideration of a number of pertinent recent studies and reviews that fail to support various conclusions drawn by OEHHA...”

Response: Numerous citations and papers have been provided to OEHHA by Philip Morris USA and others commenting from the tobacco industry and public health community. The nature of documents referenced or copied to OEHHA varies widely: unpublished documents not readily available to the public, meeting abstracts and proceedings papers, submissions to regulatory agencies, book chapters from text books,

newspaper articles, articles from the trade press, general review papers not specific to ETS on a variety of topics, and, finally, peer-reviewed publications on epidemiological studies on ETS impacts on health endpoints covered in the ETS report. OEHHA has reviewed the submissions to determine whether they raise new issues, or change the overall weight of evidence so as to lead to a different conclusion. Overall, the recent literature has tended to increase the overall weight of evidence for the associations described by OEHHA. Important new studies, for example, a large study just published by Kawachi and other coworkers (1997) at Harvard University investigating the association between exposure to ETS and risk of coronary heart disease, have been added to the document. Other studies just released have been acknowledged in the response to comments. Such studies add to the weight of evidence rather than alter the general conclusions or findings presented.

3. Comment Summary: OEHHA did not use “written criteria for every deliberative process” as endorsed by the RAAC... OEHHA did not indicate what criteria (if any) had to be met in order to classify data as supporting a causal association or as ‘suggestive’ of causality...”

Response: The criteria applied to judge the overall weight of evidence are provided on page 1-6. Application of criteria, written or otherwise, requires use of scientific judgment, a concept which is fundamental to risk assessment, as noted in the RAAC report, California risk assessment guidelines, documents from USEPA, NAS and others. The reasoning leading to conclusions regarding whether or not ETS causes a specific effect is provided in sections of the report where the effect is discussed.

4. Comment Summary: As recommended by the RAAC, field studies of personal exposure should be emphasized. Personal monitoring studies were not considered.

Response: This concern is addressed in our response to comments from Philip Morris on Chapter 2.

5. Comment Summary: OEHHA prepared the final draft with a preconceived position. OEHHA “clearly seems to have already determined that there would be associations [between ETS exposure and health effects] and that all the Final Draft must do is evaluate causality.” “In a scientifically unsound approach, OEHHA cites only those articles that support its contentions, rather than providing a review of *all* relevant scientific literature.” The comment goes on to provide its characterization of OEHHA’s review of data on adult asthma.

Response: It is the conclusion of the report, not a preconception, that ETS exposure is causally associated with certain adverse health effects. The associations described were initially discovered and reported by the authors of epidemiological studies, not by OEHHA. OEHHA has reviewed the relevant epidemiological literature, including that submitted by Philip Morris and others, to reach its conclusions. We note that in response

to comments raised on Chapter 6, OEHHA re-evaluated its finding regarding the impact of ETS exposure on asthma exacerbation in adults and has changed its conclusion.

6. Comment Summary: “The final draft fails to use a ‘weight of evidence’ literature review in which the domain of published literature for a given disease is assembled and evaluated; The final draft omits consideration of a number of pertinent recent studies and reviews that fail to support various conclusions drawn by OEHHA; Studies that are discussed in the final draft are merely described and not critically assessed; OEHHA’s acceptance of questionable data and assumptions from various studies precludes meaningful analyses and assessment of key issues. In the few key areas that do receive critical attention, specific criticisms are not iterated throughout the chapters or in the discussions of specific studies; Overall OEHHA seems to have applied a very low standard of scientific proof to its evaluation of ETS.”

Response: It is unclear what is meant by ‘domain of published literature for a given disease is assembled and evaluated’, so it is difficult to comment on that point. OEHHA has endeavored to carefully review the literature and present its overall evaluation based on the weight of the available evidence. Philip Morris takes issue with the sentence “a weight of evidence approach has been used to describe the body of evidence for an effect and to support a conclusion as to whether ETS exposure is causally associated with a particular effect” (first page of the Executive Summary) and finds great difference between this sentence and the one beginning on page 1-5 “a weight of evidence approach has been used to describe the body of evidence on whether or not ETS exposure causes a particular effect.” Because of the potential for misunderstanding OEHHA has replaced the sentence in the Executive Summary with that in the Introduction. OEHHA has reviewed the relevant literature in making its judgment and notes that many of the studies judged by those commenting as negative are simply non-informative, with small sample sizes, or designed in such a way that effects would not be expected.

Because the epidemiological data are so extensive, they serve as the primary basis on which findings are made. We have focused on the pertinent epidemiological studies, emphasizing those published in peer reviewed journals. OEHHA has endeavored to describe studies as objectively as possible. Regarding the reiteration of specific criticisms, OEHHA has at times used inclusive statements covering a number of studies in order to keep the size and readability of the document within reasonable bounds. This is a widely used and accepted stylistic convention.

7. Comment Summary: “A selective and incomplete review of the scientific literature necessarily leads to a biased portrayal of the scientific issue for ETS.” Philip Morris then provides 4 examples. The first example takes issue with the general paragraph in section 1.3.2 indicating that “Animal models for ETS exposure have recently been developed and a number of studies are currently underway.” It indicates that “Conspicuously absent from both the discussion and reference sections is any reference to five published animal inhalation studies on aged sidestream smoke (two chronic and three 90 day inhalation studies) that report no non-reversible effects and no statistically significant increased

tumor incidence among exposed animals, ...” Philip Morris then provides a list of 8 references, including these studies and identifying them as “Animal inhalation studies not referenced by OEHHA in final draft Chapter 1”. “It is difficult to see without mention of pertinent published studies and their results, how the Introduction’s discussion of animals studies can be deemed accurate, comprehensive, or balanced.” The second example takes issue with the sentence on page 1-3 “Few studies of this type [questionnaires] attempt to verify self reported exposures,” indicating that no references are given and pointing to 12 references submitted to OEHHA in 1995 on the exposure chapter which are not in the Final Draft. The third example takes issue with the sentence on the bottom of page 1-3 “Measurement of cotinine can also be useful for identifying active smokers, as levels differ between smokers and nonsmokers exposed to ETS by one to two orders of magnitude.” Philip Morris then indicates that only 4 of 19 studies it submitted on cotinine measurement are discussed in Chapter 2, and only one is referenced in the Introduction; it also takes issue with the statement on page 1-4 that “information on cigarette smoking by the mother is likely to provide a reasonable proxy for a young child’s ETS exposure,” indicating that “This conclusion is unwarranted by the analysis provided to OEHHA in the Philip Morris Comment on the External Review Draft Chapter 2...” The fourth example provided takes issue with the sentence on page 1-6 “Unlike most environmental contaminants, ETS-related health impacts are directly observable through studies of people in exposure situations that are also experienced by the general population.” Philip Morris takes issue with the words “directly observable”, referring to comments made on Chapter 2.

Response: The introduction was developed to orient the reader to the ETS review by laying out the structure of the report, definitions, and basic methodology. The second, third and fourth examples, refer to issues raised in previous and current comments on Chapter 2. At the beginning of the section containing the language being criticized in Philip Morris’ second and third examples, the reader is referred to Chapter 2. Regarding the fourth example, OEHHA respectfully disagrees.

Regarding the first example, the section on animal studies was intended to provide background, and not to lay the groundwork for a discussion of animal studies on ETS and lung carcinogenesis. In fact, the section on lung cancer was limited to a review of 4 epidemiological studies published since US EPA’s report. The animal studies cited by Philip Morris are briefly described below for the reader’s benefit. We note it is not usual to attempt to conclude anything definitive with regard to carcinogenic or related effects from short term studies such as the first three studies described below, which do not resemble either the standard carcinogenesis bioassay or one of the so-called “rapid” assays. The observation of hyperplastic and metaplastic changes in rat nasal epithelium is of interest, but the failure to observe tumors has neither positive nor negative impact. To quote the authors of one of the more recent papers which was identified in the comment, “Obviously, the two experiments (Coggins *et al.*, 1993; von Meyerinck *et al.*, 1989) were too short to produce a carcinogenic response in the two species that were examined” (Witschi *et al.*, 1995). While the results of these studies are relatively non-informative

regarding long term carcinogenesis, they may be of interest for comparison with the more recent studies published by Witschi *et al.* (1997), described below.

The two 6-month studies by Witschi *et al.*, (1995; 1997) were small in size and brief compared to the usual lifetime exposure protocol. However, in the second study (Witschi *et al.*, 1997) the authors have used a protocol variation from the usual short-term mouse lung adenoma assay, namely the incorporation of an extended observation period during which animals were exposed to clean air only. They also identify an effect of tobacco smoke (apparently on tumor growth) which renders the assay less sensitive to the tumorigenic effects of known carcinogens: this effect is apparent at the end of the smoke exposure period but disappears after the recovery and observation period. Since in this assay the initial tumor count is determined by macroscopic observation it is readily understandable that a cytotoxic influence might have such an effect on the study outcome. These findings also provide support for the hypothesis that environmental tobacco smoke (or at least, the mixture used to model its composition in this experiment) is a carcinogen in animals as well as humans, and an explanation for the failure of the earlier studies using the mouse lung short-term test system (Witschi *et al.*, 1995; Finch *et al.*, 1996) to detect this effect. The histological diagnosis of adenocarcinomas as well as adenoma, and other observations of hyperplastic lesions and episodes of cell proliferation are consistent with the types of neoplastic and preneoplastic changes seen in other animal models of carcinogenesis.

- a) Coggins CRE, Ayres PH, Mosberg AT, Sagartz JW, Hayes AW (1993). Subchronic inhalation study in rats using aged and diluted sidestream smoke from a reference cigarette. *Inhalation Toxicology* **5**:77-96.

A 90-day study was performed in which rats were exposed to sidestream cigarette smoke (10 mg/m³ particulate matter). No abnormal histopathological findings related to tobacco smoke exposure were noted in the lungs. Slight to mild hyperplasia of the nasal turbinate epithelium was noted: the effect was reversible.

- b) von Meyerinck L, Scherer G, Adlkofer F, Wenzel-Hartung R, Brune H, Thomas C (1989). Exposure of rats and hamsters to sidestream smoke from cigarettes in a subchronic inhalation study. *Experimental Pathology* **37**(1-4):186-189.

A 90-day feasibility study was performed in which rats and hamsters were exposed to sidestream cigarette smoke (4.3 mg/m³ particulate matter). The only histopathological changes observed were hyperplasia and metaplasia of the nasal turbinate epithelium of rats. These effects were reversible within 90 days.

- c) Teredesai A, Pruhs D. (1994). Histopathological findings in the rat and hamster respiratory tract in a 90-day inhalation study using fresh sidestream smoke of the standard reference cigarette 2R1. In: *ILSI Monographs: Toxic and carcinogenic effects of solid particles in the respiratory tract*. Eds. Dungworth *et al.* ILSI Press, Washington, DC. pp. 629-635.

Groups of twenty male Sprague-Dawley rats and twenty male Syrian golden hamsters were exposed to sidestream smoke for 7 h/d, 7 d/w for 90 days. Groups received exposure to a high concentration of smoke (6 µg/l total particulate matter), low concentration (2.1 µg/l total particulate matter), or clean air. Histopathological changes in the respiratory tract were examined immediately (10 animals from each group) or after 21 days (the remaining 10 animals). No such changes were observed in the hamster. In the rats, hyperplasia and metaplasia of the epithelia of the nose and larynx were noted, mainly in the high-exposure group. These findings mostly reversed during the 21-day post-exposure period. The authors commented that their findings are similar to those of Coggins *et al.* (1993) and von Meyerinck *et al.* (1989).

- d) Haley NJ, Adams JD, Axelrad CM, Hoffman D (1987). Sidestream smoke uptake by Syrian golden hamsters in an inhalation bioassay. *Indoor Air '87*, Volume 2. Institute for Water, Soil and Air Hygiene. pp. 161-167.

This paper reports absorption data and interim mortality in an inhalation bioassay of sidestream and mainstream tobacco smoke in male and female hamsters. The study was still in progress at the time of this report, and no histopathological or tumor incidence data are presented. It may be of interest that early mortality (3 months) was more severe in sidestream smoke exposed animals than in those exposed to clean air or mainstream smoke, although the mortality at later stages (3 - 15 months) of the study was actually lower in smoke-exposed groups than controls.

- e) Coggins CRE (1996). The OSHA review of animal inhalation studies with environmental tobacco smoke. *Inhalation Toxicology* 8:819-830.

This paper is a review, rather than a publication of original experimental data. Its primary purpose is to provide a detailed commentary on, and to express disagreement with, the review of animal inhalation studies in the report on occupational health risks from ETS by OSHA (1994). OEHHHA does not find any information in Coggins' review relevant to the current discussion, which has not been addressed either in the OEHHHA document or in other comments and responses.

- f) Finch GL, Nikula KJ, Blinsky SA, Barr EB, Stoner GD, Lechner JF (1996). Failure of cigarette smoke to promote or induce lung cancer in the A-J mouse. *Cancer Letters* 99(2):161-167.

A group of 20 female A/J mice was exposed to cigarette smoke (mean 248 mg total particulate matter /m³) for 26 weeks. A control group was exposed to filtered air alone. Additional groups received injections of tobacco-specific nitrosamine (NNK), alone or in combination with cigarette smoke exposure. Animals were sacrificed 5 weeks after cessation of exposure. No effects on mortality were observed, but body weight reductions, lung weight increases and carboxyhemoglobin in blood (17%) were observed in mice exposed to cigarette smoke. NNK exposed groups showed

increased macroscopic evidence of lung nodules, but exposure to cigarette smoke had no influence on tumor incidence, or multiplicity in tumor-bearing animals, either alone or in combination with NNK. The authors concluded that no effect was observed because the duration of the exposure was insufficient.

This study was relatively small in size, and the duration of exposure was brief compared to the usual lifetime exposure protocol. The power of the study to detect an effect, if an effect existed, was thus relatively low. The histological relevance of the chosen end point, a lung adenoma characteristic of this strain of mouse, to human disease has been questioned, although some other studies using this test animal and end point have been considered indicative of human cancer risk. Some of the other reported studies using strain A/J mice have observed significant lung tumorigenesis as a result of tobacco smoke (Essenberg JM [1952]. Cigarette smoke and the incidence of primary neoplasm of the lung in the albino mouse. *Science* **116**:561-562, and see the discussion of this issue in Witschi *et al.*, 1997). In view of this, and the very considerable direct evidence of lung cancer induction by cigarette smoke in humans, (see for example Doll and Peto, 1976: cited in report, Chapter 7.), this study does not provide substantial evidence to the contrary, but rather identifies the well-known difficulties of evaluating these effects in animal studies.

- g) Witschi H, Oreffo VI, Pinkerton KE (1995). Six-month exposure of strain A/J mice to cigarette sidestream smoke: cell kinetics and lung tumor data. *Fundamental and Applied Toxicology* **26**(1):32-40.

Male Strain A/J mice were exposed to sidestream smoke (4 mg/m³ total particulates) from reference cigarettes 6 h/d, 5d/w for 6 months. Controls were exposed to filtered air. No increases in lung tumors relative to controls were observed, but a transient increase in cumulative labeling increase in epithelium of the intrapulmonary airways and turbinates was observed during the first 3 weeks of exposure. Increased cell proliferation was noted at the 9th and 16th week in the turbinates. Examination of DNA modifications to K-ras in tumors from exposed and control mice suggested that exon 2 (codon 61) of this gene might be a specific target of mutagenic chemicals in sidestream smoke. The authors concluded that, if a carcinogenic effect of sidestream smoke did exist in this test system, the duration of the exposure was too short and exposure concentration too low to reveal it.

- h) Witschi H, Espiritu I, Peake JL, Wu K, Maronpot RR, Pinkerton KE (1997). The carcinogenicity of environmental tobacco smoke. *Carcinogenesis* **18**(3):575-586.

Groups of 24 male Strain A/J mice were exposed to a mixture of sidestream and mainstream smoke from reference cigarettes designed to duplicate the composition of environmental tobacco smoke (87 mg/m³ total particulates). Exposures were for 6 h/d, 5d/w for 5 months. One such group was killed and examined for lung tumors immediately, whereas a second group was then exposed to filtered air for 4 months before examination. Other groups examined the effect of tobacco smoke exposure on

carcinogenesis by urethane or 3-methylcholanthrene. Controls received filtered air only. Additional studies addressed the effect of simultaneous exposure to tobacco smoke and dietary butylated hydroxytoluene (BHT). These included a group which received tobacco smoke (52.6 mg/m³) for 2.5 months and filtered air only for a subsequent 6.5 months, plus a group receiving tobacco smoke exposure and 0.5% BHT in the diet, plus corresponding controls.

Immediately after smoke exposure more lung tumors were observed in the exposed group, but the effect was not statistically significant (exposed 6/24, controls 2/24). However, in the group where an extended observation period followed exposure to smoke for 5 months at 87 mg/m³, the increase in incidence of lung tumors was statistically significant (exposed, 20/24; control 9/24, $P < 0.005$, Fischer's exact test). In the group where an extended observation period followed exposure to smoke for 2.5 months at 52.6 mg/m³, the increase in incidence of lung tumors was of marginal statistical significance (exposed 28/38; control 23/41, $P < 0.08$, Fischer's exact test). In both these groups the tumor multiplicity was also increased significantly ($P < 0.05$, Welch's alternate t-test). Tumors were identified as macroscopically visible lesions on the surface of the lung. On histological examination, proliferative lesions in the lungs were diagnosed as focal alveolar hyperplasia, alveolar/bronchiolar adenomas and bronchiolar adenocarcinomas.

Exposure to tobacco smoke in addition to the known carcinogens urethane and 3-methylcholanthrene actually inhibited the appearance of tumors immediately after the exposure period, relative to the positive controls, but this effect disappeared at the end of the 9-month period including extended observation. Statistically significant responses to dietary BHT were not observed in either smoke or air exposed mice.

In other studies on these experimental groups, no changes in morphometric parameters of lung parenchyma were observed as a result of smoke exposure, but morphological changes and increased cell proliferation were observed in the nasal septum. Immunocytochemical staining revealed an increase in cytochrome P450 1A1 (but not 2B1 and 2E1) in lungs of smoke exposed mice examined immediately after exposure. This effect disappeared in those mice allowed a recovery period exposed to filtered air only. In parallel experiments, cumulative labeling indices indicated increased rates of cell proliferation in the airways and alveolar zone of the lungs of smoke exposed mice during the first 2 weeks of exposure.

The authors concluded on the basis of these data that environmental tobacco smoke is a pulmonary carcinogen in strain A/J mice.

8. Comment Summary: "The final draft does not meet the RAAC recommendation that uncertainties ... should be reported."

Response: OEHHHA described uncertainties, both qualitatively and quantitatively (for example, through the provision of confidence bounds on relative risk estimates). The

general issue of compliance with RAAC recommendations is dealt with at greater length in the response below to technical comments from McLaren-Hart/Chem Risk.

Stuart Brody (University of Tübingen) for Philip Morris

1. Comment Summary: Self-reporting is an unreliable method for determining the status of subjects in epidemiological studies, especially in the case of behaviors such as smoking which are perceived negatively by the subject. General issues related to accuracy of questionnaire responses are described, such as how items at the beginning of a questionnaire influence later answers, misunderstanding of the questions due to poor language fluency, cooperation and intentional misreport, impact of personality and psychiatric factors, ‘social desirability responding’, retention of information (quoting “as a rule of thumb, up to 50% of an event is likely to be forgotten after 20 minutes. After 20 hours as much as 75% of the event will be forgotten”). The commentator then reviews the literature on self reported nonsmoking and concludes that “The percentage of smokers who present themselves as nonsmokers varies between studies, but is typically of order 15-20%”. He concludes that “There is considerable research literature that indicates that self-report of smoking behavior is not valid without supporting biochemical validation. Inferences which are based on self-reports without biochemical validation are of low validity as well.”

Response: This potential problem with classification of subjects is well-known, and has been discussed in the OEHHHA report and comments, by USEPA (1992) and by individual study authors. It is for this reason that other methodologies (including use of biomarkers such as cotinine) are often employed in addition to interviews or questionnaires. The influence of this possible problem was considered in reaching the final conclusions of the OEHHHA report.

The 1986 National Research Council report and a subsequent paper, Wald *et al.* (1986) pointed out that because smokers tend to marry smokers, if a study contains smokers who are misclassified as nonsmokers, they are more likely to be classified as exposed to ETS. Therefore, the estimate of relative risk to ETS exposure will be exaggerated due to the association of lung cancer with active smoking for this group of misclassified subjects. Wald *et al.* (1986) estimated the proportion of ever-smokers who are misclassified as lifelong nonsmokers to be about 7%. This estimate was based on the percent of self-reported nonsmokers (2.1%) who have levels of nicotine and cotinine in the range of those of smokers and the percent of smokers who on subsequent re-interview claimed to have never smoked (4.9%). Lee (1986, 1989, 1991) has argued that the extent of this misclassification bias is higher, about 12%. Two recent studies (Riboli *et al.*, 1995; Nyberg *et al.*, 1997), using different methodologies, conclude that, while there is some misclassification of smokers as nonsmokers, the misclassification rate is low and is unlikely to explain the lung cancer risk from ETS exposure. The study methods and findings from these studies are summarized below.

Riboli *et al.* (1995) reported the results of a multicenter (13 centers) international (10 countries) study organized by the IARC to validate self-reported exposure to ETS from different sources by analysis of urinary cotinine levels. Questionnaire data and urine samples were collected from 1,369 nonsmoking women who had not used any tobacco products for at least 2 years. Forty-seven women had urine cotinine levels above 50 ng/mg creatinine, a level used to discriminate smokers from nonsmokers in some previous studies. Further investigation of these 47 women showed that 27 had levels between 50-150 ng/mg while 20 had levels exceeding 150 ng/mg. In fact, the majority of women (16 of 27) with levels between 50-150 ng/mg had reported long daily exposure to ETS (i.e., > 5 hours per day) 4 to 8 days prior to sample collection and were exposed to at least 8 cigarettes per day. On the other hand, a significantly lower percent of women with cotinine levels exceeding 150 ng/mg had long daily exposure to ETS or were exposed to at least 8 cigarettes per day. These investigators concluded that most of the women with levels between 50 to 150 ng/mg were truly heavily exposed to ETS while those with levels above 150 ng/mg were more likely to be deceivers and may have smoked. Thus the percent of deceivers (1.5%, 20 of 1,369) in this cross-sectional study is quite comparable to that reported by Fontham *et al.* (1994) in which 0.6% of lung cancer cases (2 of 356) (prescreened for smoking status on the basis of medical history and other factors) and 2.3% of population controls (25 of 1064) showed cotinine/creatinine concentrations of 100 ng/mg or higher. Results from this study also illustrate that cotinine levels between 50-150 ng/mg are quite plausible when nonsmokers are very heavily exposed to ETS.

Nyberg *et al.* (1997) investigated misclassification rates in two large Swedish cohorts in which smoking habits were assessed on two separate occasions some 6 to 10 years apart. Two types of misclassification rates were presented. The first misclassification rate was calculated based on the number of ever smokers misclassified as never smokers divided by the total population of ever-smokers. The second misclassification rate was calculated based on the number of reported never smokers who really were smokers divided by the total population of never smokers. In this study, the proportion of ever smokers misclassified as never smokers was 4.9% among men and 4.5% among women in the first cohort studies; the corresponding figures in the second cohort was 5.0% and 7.3%. The misclassification rate expressed as the proportion of never smokers who really were smokers was 11.1% in men and 1.3% in women in the first cohort study and 11.5% and 2.2%, respectively, in the second cohort study. Nyberg *et al.* (1997) noted that there is good agreement in most studies in terms of the first misclassification rate irrespective of geographic area or gender of subjects. On the other hand, the second misclassification rate is much more variable from study to study and that this rate can be misleading because it is dependent on the number of nonsmokers in a particular study. Aside from the rate of misclassification, these investigators also showed that in this, as in other study populations, most of the ever-smokers who were misclassified as nonsmokers had quit smoking some time earlier and smoked less than the average smokers. Thus, this study also suggested that there is limited smoker misclassification and that misclassification bias does not explain the lung cancer risk associated with ETS exposure.

Both of these studies suggest that to a large extent, misclassification of smokers as nonsmokers can be minimized if adequate screening questions are used to ensure that former smokers are identified and are excluded from studies of lifetime nonsmokers. Although cotinine is only a marker of recent tobacco exposure, it is still useful to be able to exclude current smokers from a study. In fact, multiple sources of information and careful screening questions were used in many of the newer studies of ETS and lung cancer (such as the Fontham study) so that this source of misclassification bias has been minimized. The varying degrees of misclassification bias among the studies in the US EPA meta-analysis was recognized by the agency, and adjustments applied were consequently specific to the individual studies (US EPA, 1992, Appendix B).

Lawrence B Gratt, IWG Corporation and Willard R. Chappell, submitted for Philip Morris

1. Comment Summary: Measurements of present day exposures are much less than previous measurements.

Response: This concern is addressed in our response to comments on Chapter 2.

2. Comment Summary: The commentators criticize OEHHA for not noting some papers, including some which have appeared very recently, including papers on exposure assessment and epidemiology.

Response: OEHHA considered as wide a range of source data as possible during the preparation of the document, although some material may have been excluded where its relevance to the central theme of the document was unclear. With regard to material which became available during the comment periods after preparation of the document, OEHHA has attempted to incorporate new material which substantially affected the overall balance or quality of the final version. Not all materials can be extensively reviewed here or in the document report because of resource constraints. OEHHA has noted, and continues to search for, newly published work on ETS exposure and effects, and may use this in updating or extending its conclusions about ETS health effects in future.

3. Comment Summary: Cotinine is not a reliable biomarker for ETS at current exposure levels

Response: This concern is addressed in our response to comments on Chapter 2.

4. Comment Summary: Inadequate estimation procedure for proper risk management

Response: As noted in responses to other comments, the document was not intended to provide detailed prescriptions for risk management under a specific regulatory program, but rather to provide the technical and scientific background for such actions if and when they might be undertaken. In the event that such actions are undertaken, the program in

question may choose to develop additional guidance specific to the program if such is deemed desirable or required by regulations.

Thomas B. Starr, for Philip Morris

1. Comment Summary: The time available for comment on revisions to the document after the public meeting and first round of comments is insufficient.

Response: This comment was answered in detail in a letter to Dr. Starr from Dr. Becker, OEHHA Director, after consultation with the chairmen of the Air Resources Board and the Scientific Review Panel for Air Toxic Contaminants. It was not deemed necessary given the public process already accorded to this document to extend the latest comment period beyond May 5th, 1997.

RL Tweedie and MJ Merrilees, for Philip Morris

1. Comment Summary: The figures given in the OEHHA Draft for attributable numbers of cases of disease “are very much exaggerated and overstate the problem by an order of magnitude.” He cites two papers to make the point, one a draft report by an “NHMRC Working Party in Australia”, the second a paper submitted with his comments which he has coauthored with Sue Taylor of the University of Colorado. Attributable risk calculations for California are provided in an appendix to the comments supplied by Drs. Tweedie and Merrilees.

The paper by Drs. Taylor and Merrilees investigates sensitivity of attributable risk calculations to changes in parameter values for prevalence (current, ex-, and never smokers), relative risk (current, ex, and never smokers), and estimates of numbers of deaths from the disease, and for the case of lung cancer, the parameter Z (level of ETS exposure in exposed population divided by level of ETS exposure in background population). The results for lung cancer are seen to be particularly sensitive to the choice of the parameter Z. Taylor and Merrilees suggest a graphical approach (univariate box plots) to provide the viewer a better impression of the impacts than mere examination of results under extreme cases can provide. Detailed analyses are provided for the examples of ischemic heart disease and lung cancer.

In the Appendix provided by Tweedie and Merrilees, two data sources for current smoking prevalence were used, one published on the United States Behavioral Risk Factor Surveillance System *MMWR* (1996; 45:962-963), a second from Pierce *et al.* (1994; *Tobacco Use in California. An Evaluation of the Tobacco Control Program*, 1989-1993). The second document is cited in the OEHHA report. They generated age and sex specific data for smoking prevalence from the California data. They calculated age and sex specific rates for never and ex smokers for California by applying two methods to current smoking prevalences. Under the first assumption they assumed the ex and never smoker ratio observed for the US could be applied to California, after accounting for current smokers. Under the second assumption they applied never

smoking prevalences for Australia to the California population and estimated ex-smoking prevalences by simple differencing. For both ischemic heart disease and lung cancer they assumed the relative risk ranged from 1.05-1.35 for ETS expose non-smokers, chose ranges for the other parameters as well. We could find no indication of the value chosen for Z for these calculations. The example in the Tweedie and Merrilees Appendix reports lower values than provided in the OEHHA Introduction and Executive Summary.

Response: The work of Drs. Taylor and Tweedie is of interest in evaluating sensitivity of attributable risk calculations to parameters, and it is now referenced as an in press paper in the ETS report. We also have added caveats regarding uncertainties in attributable risk calculations in the ETS report. Regarding the particular examples provided in the Appendix, we have some major concerns. The latency period for lung cancer is such that cases today are a consequence of exposures from 10 - 30 or more years earlier. OEHHA provides cases of lung cancer today attributable to ETS exposures, yet prevalence values used in the Appendix of Tweedie and Merrilees for never, ex and from active smoking are taken from very recent studies, as may have been the case of Z. This does not seem appropriate in determining ETS impacts on current cases. In earlier decades, smoking prevalence was considerably higher and near national levels in California, and because of latency, the Z factor should be based on higher prevalence values reflective of exposures in earlier years. The case for heart disease mortality is more difficult since the impacts of past versus current exposures are less clear. A caveat to this effect has been added to the ETS report.

The Tobacco Institute

The Tobacco Institute, submitted by Clausen Ely of Covington and Burling, attorneys

1. Comment Summary: “OEHHA failed to take into account the comments of external stakeholders.” “The Advisory Committee recommended that agencies ‘seek early input into the risk assessment process from risk managers and from external stakeholders.’” “OEHHA failed to follow the RAAC recommendations and effectively denied external stakeholders the opportunity to contribute meaningfully to OEHHA’s development of the draft report.”

Response: The response to these comment is provided above in the response to comment summary #1 for Philip Morris.

2. Comment Summary: OEHHA has provided insufficient time for comment on the document and insufficient access to members of the public and “stakeholders” wishing to comment: a request for an extension of the comment period was denied.

Response: Extensive comments have been received on the *Final Draft*. Multiple comment periods, several public workshops, a public forum and separate publication and

releases of draft chapters of the document have allowed interested parties multiple opportunities for input into the process of developing the final document. For more detail on the document development process, the reader is referred to the response to comment summary #1 above for Philip Morris.

3. Comment Summary: The draft document does not adequately disclose uncertainties.

Response: Where numerical ranges for deduced parameters such as odds ratios and relative risks can be calculated, they are cited. Where qualitative conclusions are drawn, the confidence with which these are made is discussed. The strengths and weaknesses of the data are discussed at length.

4. Comment Summary: OEHHA failed to incorporate new scientific evidence in its assessment. The lack of inclusion of references submitted on Chapter 2 is noted, as well as evaluations of the Butler analysis of the Fontham *et al.* study, the 1997 study by Cardenas *et al.*, and the National Mortality Followback Study analyses by LeVois and Layard.

Response: The general response to this comment is provided in the response to comment #2 above from Philip Morris, USA. The Cardenas *et al.* (1997) study has been added to the document. The Butler reanalysis of Fontham *et al.* is discussed at length in the response to comments on lung cancer section of Chapter 7 *et al.*. The LeVois and Layard analysis of the National Mortality Followback Study is discussed in response to comments on Chapter 8.

5. Comment Summary: OEHHA failed to assess the relevant scientific studies in a balanced and even-handed manner.

Response: OEHHA has attempted to take a completely unbiased approach to the review of data, and has presented and discussed the information supporting the conclusions drawn as comprehensively as possible. For a further detailed response, the reader is referred above to the response to comments #5, 6, and 7 raised by Philip Morris. In raising this issue, the Tobacco Institute commented on the treatment of the analyses of the National Mortality Followback Study as unbalanced. Detailed criticism of the LeVois and Layard (1995) study is dealt with in this Appendix in the section on responses to comments received on Chapter 8.

Gio B. Gori, for The Tobacco Institute

1. Comment Summary: Dr. Gori provides a summary of his resume.

Response: As he suggests, OEHHA is familiar with Dr. Gori's qualifications, and thanks him for this update.

2. Comment Summary: Dr. Gori makes a number of negative judgments about the quality of the report of health effects of ETS, which may be condensed into the following: Bias in favor of a predetermined conclusion; willingness to draw conclusions when faced with less than totally overwhelming evidence; disregard for scientific method. Dr. Gori finds epidemiological methodology generally deficient and unsuitable as a decision basis for public policy. Well-known authorities such as Rothman and Bradford Hill are criticized. Dr. Gori notes there is a failure to accept modification of the conclusions of the report in response to previous comments.

Response: OEHHA has approached the issue objectively and without a preconceived bias, and has made every effort to present its review of the relevant data in as clear and understandable a form as possible. The conclusion that ETS exposure is causally related to adverse health outcomes follows from the analysis of data presented in the report, and does not represent a bias which preceded its preparation. Taking this unbiased approach, OEHHA has come to a conclusion which is broadly in line with that reached by the majority scientific opinion of academics, government and other commentators on the subject. The standards of evidence and analysis used in the report are those generally used and accepted in scientific circles, and where residual uncertainties exist (as they do in any analysis, even with the most rigorous evidential support) this is noted as appropriate. There is an extensive scientific literature examining procedures for dealing with limited, uncertain or conflicting evidence, and the weighing of different expert opinions as input into a final synthesis. Standard works such as Rothman (1986. *Modern Epidemiology*. Little, Brown & Co., Boston) and Hill (1965) for evaluating epidemiological associations are well known, and widely used and understood, by the scientific community. While recognizing the difficulty of establishing associations with small relative risks, epidemiology is suitable as a basis for drawing scientific conclusions.

The California guidelines for cancer risk assessment (DHS, 1985) clearly state that when epidemiological evidence is able to offer a reasonable conclusion, this is the most important and direct kind of evidence available. The preference of human data over animal data is also emphasized by the Risk Assessment Advisory Committee. For additional responses to comments raised by Dr. Gori, the reader is referred to the section of this Appendix on lung cancer.

Maurice LeVois and Maxwell Layard, for The Tobacco Institute

The majority of comments made by Drs. LeVois and Layard are addressed in the sections on lung cancer, cancers other than lung and cardiovascular effects in Appendix B.

1. Comment Summary: “The claim that any deaths can be attributed to ETS is without scientific merit, and the attributable risk calculations reported by CA-EPA are clearly wrong” because, for lung cancer: a) the pooled US EPA /lung cancer studies are not statistically significant, b) the ETS lung cancer relative risk estimate has decreased over time (RR = 1.08, 90%CI 0.99-1.18), c) the US EPA calculations are based on higher smoking prevalence than occurs in California. For heart disease: a) the estimates are

based on references which are out of date, b) Cal/EPA does not calculate a current pooled ETS/coronary heart disease risk estimate, c) the large numbers of CHD deaths attributed by Cal/EPA to ETS have no basis. Cal/EPA should conduct a quantitative estimate of the degree of uncertainty in its attributable risk calculation.

Response: The judgment that ETS exposure is causally associated with lung cancer and heart disease does not turn on meta-analyses. The evaluation is based on a weight of evidence approach. US EPA (1994; *Setting the Record Straight: Secondhand Smoke is a Preventable Health Risk*, EPA 402-F-94-005) notes that their “finding that secondhand smoke is a known cause of lung cancer in humans is based on all the evidence ... If the meta-analysis were removed from the report entirely, the findings would be precisely the same.” Similarly the 1986 *Report of the Surgeon General* found after weighing the evidence that “the data presented in this report establish that a substantial number of the lung cancer deaths that occur among nonsmokers can be attributed to involuntary smoking.” The 1986 National Research Council Report *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects* also concludes that “Considering the evidence as a whole, exposure to ETS increases the risk of lung cancer in nonsmokers.” OEHHA in reviewing the available evidence, including that presented in the reports by the NRC, US EPA and in the 1986 *Report of the Surgeon General* concluded on the weight of the evidence that ETS exposure causes lung cancer in nonsmokers.

The pooled estimate for relative risk from the US studies on ETS exposure in nonsmoking women identified as high quality studies (Tier I) would be larger and statistically significant (e.g., 1.3 95% CI 1.09, 1.54; see Brown 1995; *Epidemiological Studies on the Association Between Environmental Tobacco Smoke and Disease: Lung Cancer and Heart Disease*, Meridian Research, Inc., September 1995). It should be emphasized that this larger estimate is based on recently reported studies conducted in the US. Regarding the appropriate prevalence value for the calculation of attributable risk due to ETS, we note that, with the long latency period associated with lung cancer, estimates of currently occurring cases should be based on higher, past prevalence values.

Regarding heart disease, a large study just published by Kawachi and other coworkers (1997) at Harvard University investigating the association between exposure to ETS and risk of coronary heart disease suggests values of relative risks larger than those used in previous calculations of attributable risk. Those reporting regular exposure in this large study had a RR of 1.97 (95% CI=1.11-3.28). We note that the result of this large study, which was released subsequent to the release of the OEHHA final draft report and has been added to the final document, appears to be supportive of the conclusion by OEHHA.

Additional discussion regarding uncertainty in attributable risk calculations has been added to the report.

RJ Reynolds

RJ Reynolds Tobacco Company, submitted by Mary Ward

1. Comment Summary: The Cal/EPA 1997 draft is an incomplete and inadequate assessment of ETS and health because it fails to consider and analyze all readily available and relevant scientific evidence and issues raised by public comments. Cal/EPA is obligated to 1) consider all relevant studies; 2) identify the studies that comprise the best available scientific evidence; and 3) base any conclusions on the best available evidence.

Response: The same and additional issues were raised by Philip Morris, USA, and The Tobacco Institute, and the reader is referred to OEHHA responses to their comments.

William J. Butler, for RJ Reynolds Tobacco Company

1. Comment Summary: Cal-EPA has not responded to earlier comments on the studies by Brownson *et al.* (1992) and Fontham *et al.* (1994). In particular he urges that the interpretation of those studies and other recent epidemiological results be reconsidered, and that the conclusion of USEPA (1992) be reviewed.

Response: A response to comments by Dr. Butler appears in the final draft (page A27-28): the published work in question is discussed extensively in the body of the text. Further discussion is provided in the lung cancer section (Chapter 7) in this Appendix in response to Dr. Butler's comments. With regard to the validity of USEPA's (1992) conclusion, the commenter is referred to the responses to comments from Lawrence B. Gratt and Willard R. Chappell on page A27 of the document, as well as responses to other commenters in the lung cancer section (Chapter 7) in this Appendix.

2. Comment Summary: Cal/EPA's calculation and discussion of attributable risks for each of four health conditions claimed to be caused by ETS (lung cancer, heart disease, low birthweight and SIDS) should be deleted or the public comment period should be extended to allow the public more time to address these calculations and their relationships with other parts of the risk assessment document. If attributable risk calculations are to be included, additional documentation should be included so that the reader has a context in which to assess the results. At a minimum the documentation should include 1) an indication that data are "insufficient to conclude that ETS is a cause of any of these four conditions. As such no episodes of these health conditions can be 'attributed' to ETS exposure." 2) the context for the results in terms of the five points raised verbally by Dr. Butler in his verbal comments at the April 17, 1997 public forum. The first of the five points was that just raised above regarding causality; Dr. Butler does not find any of the four health conditions causally related. The second point has to do with the method used by Cal/EPA to calculate attributable risk, which ignores 'the real potential for unanticipated negative effects': "Cal/EPA must explicitly acknowledge that there is a substantial likelihood that there is no population health benefit due to reductions in ETS exposure, and indeed ETS interventions may result in unexpected negative effects

Appendix B: Comment Summaries and Responses

General Remarks, Executive Summary and Introduction

in nonsmoking populations”. The third point is that for multifactorial diseases the sum of relative risks will typically be greater than 100%. The fourth point, focusing on families with parents who do smoke results in attributable risk estimates of 7 in 10 SIDS cases, a personal indictment of those parents. The fifth point is that Cal/EPA should use language in Breslow and Day for describing attributable risk (i.e., “In the absence of such [causal] evidence, a more cautious interpretation of attributable risk measures would be in terms of the proportion of risk explained by the given factor, where explained is used in the limited sense of statistical association.”

Response: OEHHA’s conclusions regarding causality for the four health endpoints named by Dr. Butler have not changed. The potential negative impact, on for example SIDS incidence, of ceasing exposure to infants to ETS was not identified by Dr. Butler, so it is difficult to comment on the second point. Regarding the remaining three points, clarifying language on attributable risk has been added to the report.

Chem Risk, for RJ Reynolds Tobacco Company

1. Comment Summary: OEHHA has failed to (1) identify the purpose of the ETS health assessment and (2) provide explicit guidance to risk managers.

Response: The purpose and scope of the document are detailed in the preface and introductory chapter of the document. It is not the intent of the document to give risk managers any instructions on implementation of any regulations related to tobacco or its use.

2. Comment Summary: OEHHA has failed to clearly and consistently apply the October 1996 recommendations of the Risk Assessment Advisory Committee (RAAC). The information presented in the ETS draft does not conform with the procedures for performing a hazard identification, dose-response assessment, exposure assessment, and risk characterization specified by RAAC (1996). OEHHA should closely examine the RAAC (1996) recommendations and specify and/or clarify the procedures used in the ETS draft. The ETS draft was deficient in at least twenty-three recommendations contained in the RAAC Report, namely:

1. “Cal/EPA should standardize the collection and/or submission of pertinent information for hazard identification.”
2. “Cal/EPA should institute uniform processes to ensure the use of state of the art knowledge, including peer review of guidelines and individual hazard identification processes and products.”
3. “Cal/EPA should have written criteria for each process in hazard identification.”
4. “Cal/EPA should standardize the content and construction, to the extent possible, of its hazard identification products. Although some informative narrative regarding uncertainty should be provided, categorical statements should also be available for use by the risk manager.”

5. "Cal/EPA should develop a process to communicate uncertainty about hazard identification to the risk manager."
6. "Cal/EPA should institute standard definitions of both systemic or general and organ specific adverse effects. The definitions should distinguish between physiological and true adverse effect."
7. "California EPA should regularly apply mechanistic knowledge to hazard identifications."
8. "Cal/EPA should use mechanistic data in its hazard identification assessments to upgrade, downgrade, or affirm past decisions. Mechanistic data should continue to be used in making future decisions."
9. "California EPA should consistently incorporate guidelines for the treatment of chemical mixtures and concomitant exposures and for the consideration of sensitive populations."
10. "Cal/EPA should use mechanistic data in its hazard identification assessments to upgrade, downgrade or affirm past decisions."
11. "Cal/EPA should use mechanistic data consistently in evaluating and making judgments about hazards of classes of structurally related chemicals, including those chemicals that have not been adequately studied in humans or in traditional animal studies for the adverse effect in question."
12. "Publication bias and in particular the unavailability of well conducted negative studies is always a problem. It was felt that while publication was not essential to review, the presentation of material in written form suitable for peer review should be mandatory."
13. "Pertaining to uncertainties in the hazard characterization, "[t]he goals of and criteria for any accompanying narrative should be thoughtfully agreed upon and recorded and the nature of the narrative should be made consistent from report to report if possible and from process to process."
14. "For non-cancer endpoints, Cal/EPA should move aggressively to update assessments when significant new scientific data become available."
15. "Mechanisms for improving communications between risk assessors and risk managers should be developed. At the least, this could include a clear statement of uncertainty in the final risk estimate."
16. "Cal/EPA should develop guidance on the appropriate use of uncertainty factors. This guidance should consider the appropriateness of the existing data and the severity of the effect in the overall magnitude of the uncertainty, above which data should be considered unreliable for use in deriving guidance levels."
17. "Cal/EPA should strive to develop guidance for quantifying and communication uncertainty as it occurs in each step in the risk assessment process."
18. "Science gaps in risk assessment can only be addressed when regulatory agencies provide feedback to the scientific community. Mechanistic models, sensitivity analysis, and uncertainty analysis are key tools in identifying science gaps. Cal/EPA is encouraged to utilize these tools when data and resources permit." For cancer endpoints, Cal/EPA should use tools such as "pharmacokinetic models of the link between exposure and biologically effective dose (i.e., dose reaching the target tissue)."

- 19 and 20. "Cal/EPA should put more emphasis on receptor-based exposure assessment. Additional monitoring of human exposures is also needed to compliment the efforts to implement receptor-oriented exposure models."
21. "Cal/EPA should develop a means to communicate information of the consequences of exposures greater than the safe exposure level but less than exposures expected to produce frank effects."
22. "Cal/EPA should be explicit about the assumptions made regarding distribution of susceptibilities to hazards when evaluating risk. We suggest it would be useful of the Agency to encourage exploration of the problems associated with variability in susceptibility among individuals."
23. "Cal/EPA should consider evaluating whether or not users of their risk assessment understand sufficiently how the decisions regarding model choice and other factors in the risk characterization are made."

Response: OEHHA used the same process and procedures in preparing the report on health effects of exposure to ETS as were used in other risk assessments prepared in support of California public health and regulatory programs. These are consistent with the published risk assessment guidelines for cancer risk assessment, and with the various other forms of published, draft and exemplary guidance used by the State of California. As was made clear during the deliberations of the RAAC, these procedures are consistent with the requirements of good scientific practice and, broadly speaking, compatible with the procedures used by other agencies such as the US EPA in similar circumstances. Many of the proposals by the RAAC recommend use of specific procedures "when data and resources permit."

The nature of the health effects data call for a different approach for addressing exposure to the ETS mixture of chemicals than is taken for a single well-defined chemical. Many of the more specific recommendations by the RAAC can only be implemented in the latter circumstance. However, the overall process by which the conclusions of the document were reached and presented are consistent with those recommendations. The underlying uncertainties are acknowledged and described in the document, but notwithstanding these uncertainties certain conclusions can be drawn based on the overall weight of the evidence. The following responses are offered with regard to the individual RAAC recommendations cited in this comment:

Recommendations 1-4: Standard procedures already in place for Cal/EPA risk assessment practices were used in the solicitation, collection and analysis of data for the report. These guidelines, and the report itself, have received extensive internal and external peer review, including review by, *inter alia*, the Air Resources Board's Science Advisory Board and other independent scientific advisors to OEHHA and Cal/EPA.

Recommendation 4, 23: Detailed guidance for risk managers in the implementation of these conclusions under specific programs would be available from the relevant regulations and supporting documents, if and when these programs determine that action is required based on the conclusions of the report.

Recommendation 6: The specific issues in the ETS document where this is relevant are handled in a manner consistent with the recommendation.

Recommendation 7, 8, 10, 11: Mechanistic data are used in the evaluation wherever these are available.

Recommendation 9: The scope of the document is the assessment of a specific hazard, not the formulation of general guidelines. The nature and implications of ETS's mixed and variable chemical composition are extensively discussed at appropriate places throughout the document.

Recommendation 12: This issue is addressed in the document, and in responses to other specific comments.

Recommendation 13: The narrative in the report is, within the constraints imposed by the subject matter, consistent with the style, objectives and content of other Cal/EPA risk assessment documents.

Recommendation 14: This was a primary purpose, and result, of the review of recent data in the document.

Recommendations 5, 15 - 17: Uncertainties (quantitative and qualitative) are discussed where appropriate throughout the document and in responses to comments. As noted above, it is not the intent of the document to give risk managers detailed instructions on implementation of a specific regulation.

Recommendation 18: This recommendation deals with several procedures which are outside the scope of the document, due in part to the nature of the data available. In other respects, such as the use of mechanistic data where possible, the report conforms to the recommendation. Extensive opportunities for two-way communication between OEHHA and the scientific community at large have been provided.

Recommendation 19-20: Where such data are available they are described and evaluated.

Recommendation 21: This recommendation is outside the scope of the document, which is not intended to directly address program-specific responsibilities such as regulations or public education.

Recommendation 22: Where such information is available it is addressed in the report. The sections covering developmental (pre- and post-natal) and reproductive effects are an example.

3. Comment Summary: OEHHA has failed to adequately characterize ETS exposures to nonsmoking populations in California. There is insufficient information regarding

exposure evaluation to support the conclusions presented in the ETS draft. In particular the assessment:

- is not consistent with the Assembly Bill 1807 process, which “requires quantitative estimates of historic and/or potential future exposure to chemicals of interest.”
- is not consistent with U.S. Environmental Protection Agency 1992 Exposure Assessment Guidance; “OEHHA did not conduct a scenario based exposure assessment for ETS.”
- is not consistent with State of California guidance issued on hazardous waste and multimedia assessment by the California Department of Health Services in 1990 and 1992.
- is not consistent with the 1996 report of the Risk Assessment Advisory Committee.

Response: The ETS health assessment is not formally part of the AB 1807 process. Exposure information on ETS is limited by the nature of the material and the extent of the data available, but is nevertheless sufficient to support the conclusions of the report. The use of prevalence assessment instead of a scenario based exposure assessment in the report is addressed in our response to comments on Chapter 2 Exposure Measurements and Prevalence. The response to the previous comment addresses the consistency with the RAAC recommendations.

4. Comment Summary: OEHHA has failed to provide sufficient information pertaining to the weight of evidence approach used to establish the strengths and weaknesses of available epidemiologic and other scientific evidence. The lack of transparency regarding the assessment methods used by OEHHA to evaluate the available epidemiologic and other scientific evidence is a significant shortcoming that prevents a thorough peer-review of the document. In the absence of detailed information regarding the step-wise scientific method used by OEHHA to include and omit information, assertions that the examination of the available scientific evidence was conducted in a fair and unbiased manner are insupportable. For each of the different health endpoints discussed in the ETS draft, OEHHA consistently failed to either address or include sufficient documentation for the 24 desirable attributes of a meta-analysis identified by a US EPA expert working group (Blair *et al.*, 1995, *Regul Toxicol Pharmacol* 22:189-197).

Response: OEHHA disagrees with the contention that the weight of evidence approach is not transparent. The review of the evidence has been exhaustive and inclusive, and the arguments used in reaching conclusions (or not reaching a conclusion, in cases where the evidence was insufficient to achieve this) are described at length.

OEHHA staff concur with the commenter that the guidelines for meta-analysis articulated in Blair *et al.* (1995) were not explicitly referenced in the document. However, most of these 24 "principles" were in fact followed in the development of the analyses, even though specific documentation of every step and decision is not provided in the public

document. The commenter is concerned that insufficient detail was provided to replicate the analysis. Greater detail is provided in the response to comment 18 submitted by Philip Morris on respiratory effects. In addition, though all the studies included in the ETS/childhood asthma meta-analysis are referenced in the document, OEHHA staff believe that it would be helpful to the commenter (and others) to include a table of studies that were excluded after being identified as potentially relevant. Such a table will be added to the final OEHHA document.

5. Comment Summary: OEHHA has failed to clearly and consistently apply relevant risk assessment guidance for properly assessing different health endpoints. Such guidance includes:

- Risk assessment procedures for the Toxic Air Contaminants Identification Program, AB 1807, Health and Safety Code Section 39650-39671, specifically recommends consideration of all relevant data in hazard identification; consideration of threshold and non-threshold models in dose response evaluations, use of monitoring results in exposure assessment; calculations of ranges and consideration of uncertainty in risk characterization.
- Safe Drinking Water and Toxic Enforcement Act of 1986, Proposition 65, Health and Safety Code Section 25249.5 (et seq.). The risk characterization does not provide a benchmark by which OEHHA can define the extent of risk from exposure to ETS.
- 1996 Proposed Cancer Risk Assessment Guidelines, by the U.S. Environmental Protection Agency.
- USEPA Guidelines for Reproductive Toxicity Risk Assessment.
- Criteria for identifying and listing substances known to cause reproductive toxicity under California's Proposition 65.
- The International Life Sciences Institute - Nutrition Foundation (ILSI-NF) expert panel of reproductive scientists.
- Methods for the derivation of inhalation reference concentrations, U.S. Environmental Protection Agency.

OEHHA provides insufficient evidence to evaluate ETS and cardiovascular endpoints.

Response: In preparing the document, OEHHA conducted a comprehensive review of the literature relevant to identification of the health hazards associated with ETS. Where appropriate, evaluation of the data was consistent with US EPA Guidelines for Reproductive Toxicity Risk Assessment. In evaluating dose response data for non-cancer endpoints, due consideration was given to the applicability of threshold models. The use of a prevalence assessment instead of a scenario based exposure assessment in the report is addressed in our response to comments on Chapter 2 Exposure Measurements and Prevalence. Where numerical ranges for deduced parameters such as odds ratios and relative risks could be calculated, these were cited in the document. Where qualitative conclusions were drawn, the confidence with which these were made was discussed. The strengths and weaknesses of the data are discussed at length. In preparing the document OEHHA was not obliged to adhere to any of the specific guidance sources referred to, but nonetheless considers that, in the interests of consistency, it has done so insofar as is

possible given the nature of the agent and the type, quantity and quality of the data available. We note that under the Safe Drinking Water and Toxic Enforcement Act of 1986 (“Proposition 65”), it is the responsibility of the party causing the exposure to determine whether this exposure leads to a significant risk to the exposee.

OEHHA believes that the evidence discussed in Chapter 8 is sufficient to conclude that ETS is causally associated with morbidity and mortality from cardiovascular disease. For additional responses to comments raised regarding the association between ETS and cardiovascular disease, the reader is referred to the section of this Appendix on cardiovascular disease.

6. Comment Summary: OEHHA has not adequately incorporated suggestions presented by the National Research Council, Carnegie Commission on Science, Technology, and Government, and the Presidential/Congressional Commission on risk assessment and management.

These institutions suggest: (1) the methodology of risk assessment must be transparent; (2) uncertainties associated with all aspects of the risk assessment must be presented; and (3) stakeholders should play an important role in the risk assessment process. The commenter submitted the guidance documents from these groups, in addition to other guidance documents.

Response: OEHHA considers that in preparing the document it has followed principles consistent with these sources, insofar as is possible given the nature of the agent and the type, quantity and quality of the data available.

7. Comment Summary: The scientific merits of the conclusions contained in the ETS draft cannot be properly evaluated. A great deal of additional risk assessment work needs to be conducted before the information contained in the document can be useful to risk managers who need to understand the risks, if any, posed by ETS. The ETS draft is lacking since it presents ambiguous or unsupported conclusions throughout the analysis. The scientific method that regulatory agencies prescribe in recent regulatory risk assessment policy guidance is missing or incomplete. A significant amount of additional work is needed to prepare a health assessment that can be properly reviewed and evaluated by the scientific community. The guidance noted in item 6 above should be reviewed.

Response: As noted above, OEHHA considers that in preparing the document it has followed principles consistent with the guidance sources noted in comment 6, insofar as is possible given the nature of the agent and the type, quantity and quality of the data available. It is considered that there is sufficient detail presented to allow evaluation of the conclusions reached, and this contention is supported by the extent of commentary (both favorable and unfavorable) on specific issues which has been received. It is agreed that, by intention, specific regulatory programs would need to evaluate the conclusions in the light of their procedural and practical requirements, and might need to develop more

specific evaluations and guidance for their risk managers to suit their particular circumstance.

Others

Robin Hobart, Americans for Nonsmokers' Rights

1. Comment Summary: OEHHA is congratulated for its completion of the report, which is the first comprehensive report (covering health issues besides lung cancer) to appear for more than a decade.

Response: OEHHA thanks the commentator for this support.

2. Comment Summary: No specific recommendations are included in the report. Such recommendations are necessary to protect public health. Specific measures are advocated, including:

Protection from secondhand smoke exposure at work, including removing exemptions for certain occupational groups.

Specification of the limitations of ventilation systems in protecting non-smokers in public areas (such as bars and gaming clubs) where smoking may be permitted to continue.

Opposition to efforts to preempt local ordinances which are stronger, or better enforced, than statewide restrictions.

Response: The purpose of the OEHHA report is to provide the risk assessment element in the overall approach to defining and controlling the public health effects of ETS exposure. Specific risk management strategies are therefore outside the scope of this report.

Donald O. Lyman, Division of Chronic Disease and Injury Control, California Department of Health Services (CDHS)

1. Comment Summary: CDHS welcomes the report, notes its consistency with other documents released by the U.S. Surgeon General, the National Research Council, the U.S. Environmental Protection Agency and the National Institute for Occupational Health and Safety. Dr. Lyman comments that it will assist that Department in pursuing its public education and regulatory programs relating to smoking and passive smoke exposure and their impact on public health.

Response: OEHHA thanks Dr. Lyman for his comment, and will endeavor to comply with his request to release the report expeditiously as soon as the comment period and updating process are complete.

Stanley M. Greenfield

1. Comment Summary: “While the report is comprehensive and generally makes a good attempt to be unbiased and objective, there are several instances (some of which are described) where the authors demonstrate a bias towards the hypothesis of an adverse ETS impact.”

Response: OEHHHA has made every attempt to avoid any bias or preconception in preparing the report. The identification of adverse health effects from ETS exposure is a conclusion, not a bias, of the report. The instances cited appear mainly to result from cases where OEHHHA differs slightly in its interpretation of the data from that of the commentator. These are not remarkable given the acknowledged uncertainties in the data: specific matters are addressed in other comments.

2. Comment Summary: Exposure assessments are not consistent with guidance recently issued by Cal/EPA.

Response: This concern is addressed in our response to comments on Chapter 2.

(Other comments relate to specific matters in other chapters.)

Louis Rosenberg

1. Comment Summary: “After extensive exhaustive searches your report will confirm the usual scare tactics that has been prevalent from the EPA, FDA and the 300 organizations dedicated to condemn cigarette smokers. The U.S. Department of Health and Human Services published “Healthy People 2000 Review 1995-96”. The objective of this report is to CONTROL HUMAN BEHAVIOR by the year 2000... With the concerns relating to ETS. I have read the reports from EPA and CDC which used the computer generated program of mathematical formulae called ‘SAMMEC’ (Smoking Attributable Morbidity, Mortality, and Economic Cost)... Statistics were concluded towards a preconceived goal of these anti-smokers”

Response: OEHHHA makes no comment on the behavior of either smokers or non-smokers in the report, and is concerned only to support, by scientific evaluations, efforts to improve the health of both groups, in line with the Department’s mission statement. OEHHHA was unable to identify any scientific issue in this comment to which it could respond.

Jay R. Schrand

1. Comment Summary: It is proposed that a genetic predisposition towards sleep apnea is a factor in determining the propensity for tobacco (nicotine) addiction, and that this association is a confounding factor in the epidemiological findings of increased illnesses among spouses and children of smokers. To quote Mr. Schrand’s paper (*Medical*

Hypotheses 47:443-448, 1996): “We speculate that, through adaptation, long-term hypoxia may be responsible for the increased number of nicotine-binding sites in smokers ...”

Response: Mr. Schrand’s comments appear to be based on a series of unsupported assumptions and speculations. His specific speculation of a genetic predisposition takes the opposite interpretation of the data, in several cases, from that which is most usually encountered in the scientific literature. There may well be genetic factors relating the susceptibility of parents and children to various diseases, including those identified as associated with exposure to environmental tobacco smoke. However, the comments provided no quantitative assessment of the alleged relationships between predisposition to sleep apnea, nicotine addiction, and illnesses in non-smoking spouses or children, nor indication that any such effects, if they exist, are of sufficient magnitude or frequency in the subject populations to influence the results of the epidemiological studies significantly. It should also be noted that the effect of randomly distributed confounding factors is likely to dilute rather than enhance the apparent correlation between various diseases and exposure to environmental tobacco smoke. We agree with Mr. Schrand that there are a number of poorly understood but possibly relevant factors, including genetic predispositions, assortive mating tendencies *etc.*, which may affect the health experience of certain population groups. However, in the case of environmental tobacco smoke the strength of the data presented, the plausibility and economy of the primary hypothesis and the extraordinary convolutions involved in the competing hypotheses reinforce the view presented in the OEHHA document.

John Slade (Chairman, Committee on Nicotine Dependence) for the American Society of Addiction Medicine

Comment Summary: “This is a thoughtful and balanced review of the literature on ETS. It provides a very useful benchmark of scientific knowledge about this important public health problem”. Two publications were appended:

Stoddard JJ, Gray B. (1997). Maternal smoking and medical expenditures for childhood respiratory illness. *American Journal of Public Health* 87(2):205-209.
Gori G.B. (1997) Easy Target. *Tobacco Reporter* March 1997.

Response: Comment noted. OEHHA also notes with interest that the article by Stoddard and Gray (1997) reaches conclusions consistent with OEHHA’s report of health effects of ETS.

Linda Stewart

Comment Summary: It appears that the commentator is unhappy with the conclusion of the report. The commentator makes a series of accusations that the OEHHA report is biased and that California regulators or risk assessors (apparently not distinguished by the commentator) act from a financial motive (“funding bias”).

Response: OEHHA denies bias, as noted in the responses to various other comments, and has no financial motivation to draw conclusions that ETS is or is not a health hazard.

Comment Summaries and Responses on Chapter 2: Exposure Measurements and Prevalence

Philip Morris

Philip Morris, USA submitted by Richard Carchman, attorney for

1. Comment Summary: The final draft report failed to meet its stated goal of providing a review that “is based on exhaustive searches of the literature”. The final draft report does not include some of the references submitted by Philip Morris in 1995 on the External Review Draft for Chapter 2.

Response: OEHHA reviewed the papers submitted by Philip Morris and has added some of them to the chapter; other papers that are not included either do not present new information or are only marginally related to the issue being discussed.

2. Comment Summary: The final draft report does not articulate or explain its decision to base health risk predictions for ETS on pre-1992 exposure data. Its calculation (page ES-3) is too simplistic and does not take into consideration that there is a 28 percent decline in smoking prevalence in California since 1992.

Response: The report used the most appropriate exposure information available for estimating health risks associated with ETS exposure. For chronic health effects with long latency periods, past exposure information may provide more accurate estimates of current morbidity and mortality than current data. For other health effects, such as low birthweight and sudden infant death syndrome (SIDS), more recent data (e.g., data collected in 1993) were used.

3. Comment Summary: The final draft report does not have a section on exposure assessment that allows it to estimate health risks associated with ETS.

Response: A clarifying statement has been added to the chapter. Consistent with the approach used by the National Research Council (1986), U.S. EPA (1992), DiFranza (1996), and Wells (1994), the final draft report uses prevalence information in estimating risks attributable to ETS. Exposure prevalence assessment is often used by epidemiologists in estimating health risks associated with occupational and environmental hazards. Exposure prevalence is discussed in Section 2.6, Section 3.2.4.1, Section 4.2.4.1, and Section 6.1.3.5.

4. Comment Summary: OEHHA’s response to comments submitted on External Review Draft Chapter 2 (August 1995) is incomplete. Appendix A of the final draft report does not address challenges, criticisms and new data presented in the Philip Morris Comment on the External Review Draft for Chapter 2 “Exposure Measurements and Prevalence” (1995).

Response: Philip Morris highlighted several issues as examples; these are summarized sequentially in Comment Summaries 5-10 below.

5. Comment Summary: None of the carcinogens listed in Chapter 2 has been demonstrated to be carcinogenic to any human tissue or to the lung tissue of experimental animals.

Response: Benzene, arsenic and chromium (VI) have been identified by US EPA as human carcinogens. Other chemicals listed in Table 2.2 of Chapter 2 have been shown to cause cancer in laboratory animals. The most common route of administration is through the oral route. Since most of the cancers (e.g., liver, kidney) caused by the listed chemicals are not at the site of entry, there is no reason to believe that the observed carcinogenic effects are specific to the oral route. As discussed in Chapter 7 of the report, in addition to lung cancer, there is evidence indicating that tobacco smoking is associated with leukemia and cancers of the kidney, pancreas, oral cavity, esophagus, stomach, and bladder (IARC, 1986; U.S. DHHS, 1989).

6. Comment Summary: The findings of health effects for ETS are based upon epidemiological results that are determined by proxy markers (e.g., marriage to a smoker or having a parent who smokes). However, cohabitation with a smoker does not imply exposure to ETS. In addition, a proxy marker provides no information on intensity, duration or frequency of ETS exposure.

Response: Although a small percentage of subjects who live with a smoker may have low or no exposure to ETS, the effect of this type of misclassification is likely to weaken the observed association between ETS exposure and adverse health effects, not strengthen it. Many epidemiological studies cited in the report did obtain and use information that indicates the intensity or duration of ETS exposure. Some of the common measures are: number of smokers in the house, number of cigarettes smoked by the smoker in the house, and number of years the subjects have lived with a smoker.

7. Comment Summary: Chapter 2 suggests that MS and SS are mutagenic and genotoxic mixtures, yet many studies fail to show that ETS, at normally encountered levels, is either mutagenic or genotoxic.

Response: A number of papers (Holz, 1993; Lee *et al.*, 1992; Lee *et al.*, 1993; Autrup, 1996) submitted by Philip Morris (in their Attachment D) reported that tobacco smoke and ETS produce DNA adducts and chromosomal aberrations in humans and laboratory animals. These data show that MS and SS are mutagenic and genotoxic.

8. Comment Summary: Studies have shown that ETS concentrations have declined from 1992 to the present. These studies indicate that concentrations of ETS constituents in the air of homes, public places, and workplaces are typically *de minimis*.

Response: The recent decline in smoking prevalence in California is discussed in Section 2.6.4.3 and Section 2.6.4.4 of Chapter 2. Though ETS exposure in some segments of the general population has decreased in recent years, the health risks associated with ETS are not trivial and cannot be ignored. It is not clear what the commentator meant by “de minimis”, or what criteria were used to reach this conclusion. Also, a recent decrease in ETS exposure does not guarantee that exposure will not increase again in the future.

9. Comment Summary: Single-point measurements are used in virtually all of the published studies on cotinine, and reported concentrations have been interpreted as quantitative measures of ETS exposure. Such measures do not provide assessments of exposure due to intra- and inter-individual variations.

Response: Chapter 2 describes several analytical methods, such as the measurement of nicotine and RSP in air, and cotinine in body fluids, that are commonly used for monitoring short-term ETS exposures. However, these methods are less useful for estimating long-term exposure to ETS.

10. Comment Summary: Relative contributions of ETS constituents to an individual’s total exposure from all sources are minimal.

Response: There are recent monitoring data showing that ETS could contribute a significant percentage of volatile organic compounds to an individual’s total exposure. Hodgson *et al.* (1996), using 3-ethenylpyridine as a tracer, investigated the contribution of ETS to the measured volatile organic compounds in several smoking areas. They estimated that ETS contributed 57-84% of the formaldehyde concentrations, 43-69% of the 2-butanone concentrations, 37-58% of the benzene concentrations, and 20-70% of the styrene concentrations.

11. Comment Summary: Chapter 2 does not use measurement data, area monitoring or personal monitoring, to estimate “exposure”. Instead, ETS exposure data are derived from questionnaires which suffer from misclassification.

Response: The purpose of Chapter 2 is to provide background information about methods and approaches researchers use for monitoring short-term ETS exposure, and to provide information on prevalence. The chapter also provides some average and maximum levels of ETS markers measured under various exposure conditions. The short-term exposure data obtained from these methods are of limited use in estimating adverse health effects that are associated with long-term ETS exposure. This report uses the approach of prevalence assessment in estimating adverse health effects associated with ETS. The same approach is recommended by NRC (1986) and US EPA (1992).

12. Comment Summary: The final draft report said that “studies on the reliability of questionnaire responses indicate that qualitative information obtained is generally reliable, but that quantitative information may not be.” Yet this does not discourage OEHHHA from using information quantitatively in the Final Draft.

Response: The report said that some of the quantitative information obtained from questionnaires are useful but less reliable than qualitative information. However, we do not agree with Philip Morris' claim that the quantitative data are inaccurate and unreliable. Some questionnaires have provided reliable quantitative information (e.g., Coghlin *et al.*, 1989).

13. Comment Summary: Philip Morris suggested that there are data indicating that it is the unattached, gaseous fraction of radon and not those attached to smoke particles that determines the amount of radiation to which the respiratory tract is exposed. Since ETS reduces the gaseous fraction of radon, Philip Morris argued that ETS could reduce the radiation dose from radon.

Response: ETS enhances the concentration of airborne particles, thereby reducing the unattached fraction of the short-lived decay products of radon. However, the mobility of such particles is much less than for the unattached fraction, with the result that more of the decay products remain airborne for longer periods. Thus, the presence of ETS may either reduce or enhance the dose, depending on the prevailing suspended particle levels in the absence of ETS (Pritchard, 1990).

14. Comment Summary: The California Air Resources Board study was conducted in 1987 and 1988. The data are nearly a decade old and cannot be used to represent current ETS exposure in California. Philip Morris also cited two more recent studies that show lower exposure to ETS.

Response: The California Air Resources Board study and California Adult Tobacco Surveys sponsored by the California Department of Health Services conducted in 1990, 1992 and 1993 provide the information presented in Chapter 2 specific to California. One of the papers cited by Philip Morris is an unpublished submission to US OSHA by Healthy Buildings International (1994). The other paper (Clayton *et al.*, 1993) reported that during the day about 36% of the non-smoking subjects in the study were exposed to ETS (Table 7 of the paper). Though the study was designed to slightly oversample passive smokers relative to the survey population, the result showed that the prevalence of ETS in Riverside, California in the fall of 1990 is similar to the values described in the final draft report. We could not find the information cited by Philip Morris that Clayton *et al.* reported that "study participants spent less than 2 percent of their time in the presence of smokers."

15. Comment Summary: Philip Morris suggests measurements of respirable suspended particulates (RSP) tend to overestimate contributions of ETS because of the wide number of sources of RSP in indoor and outdoor environments. Over the past 10 years, better methods have been devised to more accurately reflect the contribution of ETS-related RSP to the total RSP. Those methods include UVPM, FPM and solanesol.

Response: The text on page 2-6 is not in conflict with Philip Morris' comment.

16. Comment Summary: Philip Morris suggested the discussion on the formation of DNA adducts when benzo[a]pyrene diol epoxide is mixed with human bronchial epithelial cells is uncritical and potential criticisms are not assessed.

Response: It has been demonstrated that benzo[a]pyrene is metabolized by the oxidative enzyme systems into benzo[a]pyrene diol epoxide. It is generally believed by the scientific community that benzo[a]pyrene diol epoxide causes genetic damage and cancer (IARC, Vol 32. Polynuclear Aromatic Hydrocarbons, Part I, 1983; ATSDR Toxicological Profile for Benzo[a]pyrene, 1990). The purpose of this study is to show that DNA damage caused by benzo[a]pyrene is similar to the type of DNA adducts that are found in human lung cancer tissues obtained from smokers. The criticisms raised by Philip Morris cannot be used to explain the results of the study.

17. Comment Summary: Chapter 2 (pp. 2-28 to 2-31) relies on a number of cotinine studies to illustrate ETS exposure prevalence over the past 15 years. All of the studies relied upon single-point measurements of cotinine which are incapable of providing accurate quantitative information about ETS exposure.

Response: Almost all the studies cited in pp. 2-28 to 2-31 used interviews or questionnaires to obtain long-term ETS exposure data. Some of the studies also used supplemental information such as cotinine levels measured in serum or urine to confirm and validate the ETS exposure data. A large number of single point measurements can provide useful information regarding the extent and distribution of exposure.

18. Comment Summary: Philip Morris suggested that because of the very low limits of cotinine detection employed, the CDC study (pp. 2-28) could not effectively discriminate between ETS-exposed and nonexposed individuals.

Response: This is merely speculation on the part of Philip Morris. A method with a low detection limit can characterize cotinine levels in body fluids better than one with a high detection limit. One of the goals of the CDC study was to investigate the correlation between ETS exposure and cotinine levels.

Lawrence B. Gratt, IWG Corporation, for Philip Morris

1. Comment Summary: Although OEHHHA acknowledged receipt of our comments, there was no response. Dr. Gratt re-submitted his paper to US OSHA titled “Environmental Tobacco Smoke Exposure in the Present-day Workplace: Analysis and Implications for OSHA’s Risk Assessment” to OEHHHA. There are two main points in the paper: (1) present-day ETS workplace exposure is estimated to be much less than past exposure from living with a smoker, and (2) cotinine in body fluids is not a useful biomarker for ETS at present workplace exposures.

Response: It is likely that due to the increased restriction on smoking at workplaces, recent ETS exposures at some worksites are lower than those in the past. However, we do not agree that this makes cotinine not useful as a biomarker for ETS exposure. Furthermore, there are monitoring data indicating that recent measures of airborne nicotine at workplace are much higher than those cited by Dr. Gratt (see our response to other comments of Dr. Gratt in other sections of Appendix B).

2. Comment Summary: Benowitz (1996) argued that diet is an insignificant source of nicotine. His arguments are predicated on the assumption of a typical nicotine dose of 80 µg/day. But based on our calculations, this is four times the 90th percentile values for the present day exposures. The cause of this overprediction may be nicotine in the diet, e.g., tea.

Response: Jenkins *et al.* (1996) used personal sampling technology for measuring ETS exposure of approximately 100 nonsmoking subjects in each of 16 cities in the United States. They monitored four groups of people: (i) ETS exposure at work and away from work, (ii) ETS exposure away from work, (iii) ETS exposure at work, and (iv) no reported ETS exposure; they found the mean 24-hr time weighted average airborne concentration of nicotine for the four groups were 3.3 µg/m³, 1.4 µg/m³, 0.7 µg/m³, and 0.06 µg/m³, respectively (Table 6 of the paper). Assuming an inhalation rate of 20 m³/day and 100% absorption, estimated mean nicotine dose due to ETS for the four groups are 66 µg/day, 28 µg/day, 14 µg/day, and 1.2 µg/day, respectively. These data indicate that the estimation (80 µg/day) used by Benowitz is reasonable and supported by the personal monitoring data (66 µg/day) reported by Jenkins *et al.*

For a discussion on dietary source of nicotine, see our previous response to public comments.

3. Comment Summary: Tunstall-Pedoe *et al.* (1991) reported that tea drinking is not a significant source of nicotine. But the report based its conclusions on serum cotinine measurements that were mostly less than 1 ng/ml. Of the 40 serum cotinine levels reported by Tunstall-Pedoe *et al.*, 28 were less than 1 ng/ml, 10 were between 1 and 2 ng/ml, and none were greater than 2.5 ng/ml. This study used a method developed by Feyerabend and Russell (1980) who reported a reproducible lower limit of 1 ng/ml.

Response: The serum cotinine levels reported in Table 1 of the paper are median values. There are 3383 nonsmoking men and women in the study, and the researchers measured serum cotinine levels of every subject. They found a consistent increase in median cotinine level with passive smoking. No such relationship was observed between median cotinine level and tea consumption. However, they reported that there is a possible increase in serum cotinine in those who drank 10 or more cups of tea a day.

4. Comment Summary: Recent studies by Jenkins, *et al.* (1996), O'Connor, *et al.* (1993) and Ogden, *et al.* (1993) show that present-day exposure to ETS outside of home or work

are very small. Ogden reported a nicotine concentration of $0.08 \mu\text{g}/\text{m}^3$ for the 24 hr TWA for those reporting no exposure at home or work.

Response: The data cited by Dr. Gratt indicate that the most important sources of ETS exposure are at home and workplace.

5. Comment Summary: Dr. Gratt cited a number of studies showing that nicotine concentrations measured by Phillips (1994 and 1996), Jenkins (1996), Ogden (1993) and O'Connor (1993) are within the range of 0.08 to $0.51 \mu\text{g}/\text{m}^3$. Some of the measurements were taken from homes and others from workplaces. At these ETS exposure levels, Dr. Gratt argued that cotinine from ETS is much less than those from dietary sources.

Response: As discussed in the final draft report, one characteristic of ETS markers is that they exhibit extreme spatial and temporal variability. The measured concentration of ETS markers at a given setting depends on many factors including rate of tobacco consumption, room size, the placement of air monitors, the ventilation rate, air mixing and removal of contaminants by air filters or deposition. Hammond *et al.* (1995) recently measured 25 worksites, including offices and production areas. Among closed offices, the median weekly nicotine concentrations measured at nonsmokers' open desks in companies that allowed smoking, companies that restricted smoking, and companies that banned smoking were 8.6 , 1.3 , and $0.3 \mu\text{g}/\text{m}^3$, respectively (averages were 14 , 3.4 , and $0.7 \mu\text{g}/\text{m}^3$, respectively). Similarly, the median weekly nicotine concentrations measured in nonsmokers' work areas in the production areas were 2.3 , 0.7 and $0.2 \mu\text{g}/\text{m}^3$ for worksites that allowed smoking, restricted smoking, and banned smoking, respectively, and the corresponding means were 4.4 , 2.2 , and $0.2 \mu\text{g}/\text{m}^3$. These data show that recent ETS exposures at the workplace are significant except in places where smoking is banned.

Daniel T. Lackland, for Philip Morris

1. Comment Summary: The final draft report includes "measures" of ETS exposure based on proxy and self-report in the same capacity as factors, such as blood pressure levels, which have been appropriately measured. These weak measures are of particular concern because more accurate levels of ETS can be determined by area or personal sampling.

Response: The information used represents the best long-term measures of ETS exposure currently available.

RJ Reynolds

RJ Reynolds Tobacco Company, submitted by Womble, Carlyle, Sandridge and Rice, attorneys

1. Comment Summary: Since the release of the last draft titled “Environmental Tobacco Smoke: Exposure Measurements and Prevalence” in August 1995, additional studies have been published that provide new information that Cal/EPA must consider as it attempts to revise the chapter on ETS Exposure Measurements and Prevalence in its 1997 Draft. RJR suggested 14 publications for Cal/EPA to consider.

Response: OEHHA reviewed the papers submitted by RJR and included a number of them in the final draft report.

2. Comment Summary: 3-Ethenylpyridine (3-EP) is a better marker than nicotine for the ETS vapor phase and FPM and UVPM are better markers than RSP for the ETS particle phase.

Response: The limitations of nicotine and RSP as markers of ETS have been discussed in the chapter. The discussion on the application of 3-EP, FPM and UVPM for monitoring ETS has been revised.

3. Comment Summary: Butler reported that the value of the Z-factor he calculated from NHANES III study was approximately 4.8, almost three times higher than the value (1.75) used by US EPA. If a Z-factor value of 4.8 is used, it would decrease by more than half the number of lung cancer deaths statistically attributed by US EPA to ETS.

Response: As Philip Morris and RJR Reynolds have stated, ETS exposure has declined in recent years, so one would expect the current Z-factor to be greater than the Z-factor of the past. Since it takes many years for lung cancer to develop, for this particular end-point, it may be appropriate to use historical ETS exposure data rather than the more recent data to derive the Z-factor in attributable risk calculations for cases currently occurring in California.

ChemRisk, for RJ Reynolds

1. Comment Summary: The exposure assessment performed for this document does not comply with available exposure assessment guidance nor with the “Review of the Cal/EPA’s Risk Assessment Practices, Policies, and Guidelines”. Although ETS exposures can be quantified based on available monitoring data and using a scenario-based exposure assessment approach, OEHHA did not conduct a scenario-based exposure assessment for ETS.

Response: A clarifying statement has been added to the chapter. Consistent with the approach used by the National Research Council (1986), U.S. EPA (1992), DiFranza (1996), and Wells (1994), the final draft report uses prevalence assessment for the estimation of health risks associated with past or recent exposure to ETS.

Others

Gordon Fung, American Heart Association, submitting comments by Neal L. Benowitz, University of California, San Francisco

1. Comment Summary: The half-life of cotinine is stated to be 20-30 hours. More recent data indicate an average half-life of about 16 hours.

Response: The estimated half-life of cotinine in body fluids has been revised.

Michael P. Eriksen, U.S. Department of Health and Human Services

1. Comment Summary: Page 2-12, paragraph 4, refers to an estimated half-life of cotinine in nonsmokers of 24-48 hours which is notably longer than the commonly cited half-life of about 15-20 hours.

Response: The estimated half-life of cotinine in body fluids has been revised.

2. Comment Summary: Relatively large variability has been reported among studies that measured cotinine concentrations in urine. This is because multiple nicotine metabolites are present in urine and various analytical methods may differ markedly in their specificity.

Response: The text on page 2-13 has been revised to highlight this concern.

3. Comment Summary: Another reason why sometimes cotinine in body fluids fails to distinguish between self-reported unexposed and ETS-exposed nonsmokers is that most methods used for cotinine analysis, particularly using blood or saliva samples, are simply not sensitive enough.

Response: The text on page 2-14 has been revised.

4. Comment Summary: In Table 2.3, page 2-48, the heading “Urine (ng/ml creatinine)” should be given as “Urine (ng/mg creatinine)”. Also many of the articles cited in the tables from Chapter 2 are not included in the list of references at the end of the chapter.

Response: The suggested change has been made. Articles cited in the tables have been added to the list of reference.

Stanley M. Greenfield

1. Comment Summary: The exposure assessment performed for this document do not comply with the recently issued Cal/EPA “Exposure Assessment and Stochastic Analysis Technical Support Document” nor with the “Review of the Cal/EPA’s Risk Assessment Practices, Policies, and Guidelines”.

Response: A clarifying statement has been added to the chapter. Consistent with the approach used by the National Research Council (1986), U.S. EPA (1992), DiFranza (1996), and Wells (1994), the final draft report uses prevalence assessment in estimating health risks associated with exposure to ETS. Prevalence assessment is often used by epidemiologists for the estimation of other occupational and environmental health risks.

Otto J. Mueksch

Comment Summary: In a special report in Consumer's Research (April 1992), "Passive Smoking and Your Heart", three doctors said none of the nine epidemiological studies actually measured exposure to ETS, but rather projected or estimated an exposure to ETS on the basis of a surrogate.

Response: This is true, but does not negate the validity of the studies.

Wayne R. Ott, Stanford University

1. Comment Summary: The chapter does not cite a number of important studies on measurements and models of human exposure to ETS that were done in California.

Response: Some of the studies recommended by Dr. Ott have been added to the chapter.

2. Comment Summary: Dr. Ott does not agree with the statement "... the extreme spatial and temporal variation of ETS concentration indoor and outdoor environments..." makes it "... not feasible, technically and economically, to accurately determine the long-term ETS exposure history of an individual."

Response: We have not seen any scientific paper that has measured or modeled the long-term ETS exposure (e.g., a few months to a few years) of a target population.

James L. Repace

1. Comment Summary: The exposure chapter needs to be expanded to include information on ETS models.

Response: The purpose of the chapter is to summarize some of the commonly used methods for measuring ETS markers and biomarkers. This information is useful as ETS marker and biomarker results are often used to validate questionnaire and interview findings. We do not feel a detailed discussion of ETS models is warranted in this chapter. Nevertheless, the chapter has been revised to acknowledge the recent advances in the modeling of ETS markers in air.

Linda Stewart

1. Comment Summary: “Since cotinine is *not* an apparently good marker, *nor* harmful in itself, then *why* is it so consistently and flashily used as a marker ... for the stuff that it *doesn't* mark?”

Response: Though cotinine does not correlate perfectly with many ETS constituents, it is still considered to be an useful biomarker for current ETS exposure by most scientists in the field.

2. Comment Summary: “You’re apparently aware of the peer-reviewed papers by Domino et al, in which an ounce-and-a-half of potatoes yields the cotinine equivalent of a drink in a smoky room, and yet ... where is that mentioned?”

Response: This comment was previously raised and considered. The reader is referred to two recent papers for more information on the use of cotinine as a biomarker of ETS exposure (Repace, *et al.*, Risk Analysis, 15 (1), 1995; Benowitz NL, Epidemiol Rev, 18 (2), 1996).

3. Comment Summary: “You note (2-7) that “the highest nicotine concentrations in indoor environments were measured in bars and in smoking sections of airplanes, with levels reaching as high as 50 to 75 $\mu\text{g}/\text{m}^3$. Yet DOT (P 15-89-5, 1989) shows a documented average of 13.4 $\mu\text{g}/\text{m}^3$ in the smoking sections of planes.”

Response: Airborne nicotine concentration due to ETS is highly variable, spatially and temporally. It depends on a number of factors including rate of tobacco consumption, room size, the placement of air monitors, the ventilation rate, air mixing and removal of contaminants by air filters or deposition. As stated in the chapter, most average concentrations of nicotine range about 100-fold, from 0.3 to 30 $\mu\text{g}/\text{m}^3$. The value reported by DOT is within this range.

4. Comment Summary: “I’ll refer you to the government’s own report in which nicotine levels in the non-smoking sections on the planes that allowed smoking were ... virtually nil on the majority (up to 82.6%) of the flights, and where it was detected, the amounts were amazingly small. And in fact, DOT admitted, quite similar to the levels on ... the no smoking flights, which, it said further, in most cases fell below the level of detection (DOT 1989, P 4-25).”

Response: The report (DOT, 1989) cited by Linda Stewart is not included in the reference list provided by her. The information cannot be verified. However, we found two published studies on ETS levels in the smoking and non-smoking sections of commercial aircrafts. Oldaker and Conrad (Envir Sci Technol, 21, 994-999, 1987) reported that the average vapor phase nicotine levels were 22.4 $\mu\text{g}/\text{m}^3$ in smoking sections, 10.6 $\mu\text{g}/\text{m}^3$ in the boundary region of no-smoking sections, and 3.3 $\mu\text{g}/\text{m}^3$ in the remainder of the no-smoking section. Nagda *et al.* (Atmospheric Environment, 26A (12)

2203-2210, 1992) monitored ETS marker levels on 92 randomly selected flights. There were 23 non-smoking flights and 69 smoking flights. They reported that average RSP (by gravimetric and optical methods) were 175.8 $\mu\text{g}/\text{m}^3$ in the smoking sections, 53.6 $\mu\text{g}/\text{m}^3$ in the boundary sections, 30.7 $\mu\text{g}/\text{m}^3$ in the middle sections, and 35.0 $\mu\text{g}/\text{m}^3$ in the remote sections of smoking flights. By contrast the average RSP levels measured in the rear and middle sections of non-smoking flights were 34.8 $\mu\text{g}/\text{m}^3$ and 40.0 $\mu\text{g}/\text{m}^3$, respectively. They also reported that average gas-phase nicotine levels were 13.4 $\mu\text{g}/\text{m}^3$ in the smoking sections, 0.26 $\mu\text{g}/\text{m}^3$ in the boundary sections, 0.04 $\mu\text{g}/\text{m}^3$ in the middle sections, and 0.05 $\mu\text{g}/\text{m}^3$ in the remote sections of smoking flights. By contrast the average nicotine levels measured in the rear and middle sections of non-smoking flights were 0.0 $\mu\text{g}/\text{m}^3$ and 0.08 $\mu\text{g}/\text{m}^3$, respectively.

5. Comment Summary: “You admit (on 2-6) that respirable particulates are common, ... and yet continue to use them as markers. And in fact, these particulates got smokers bounced from the air. And yet lo and behold this: (Direct quote, Consumer Reports, 8/1/94). A recent industry study documented surprisingly high levels of particulates aboard the tested planes. [These were planes on which nobody had a smoke in four years.] The planes averaged more than twice the level found in the 1989 [DOT] government study.”

Response: As discussed in the chapter there are limitations in using respirable particulates as a marker for ETS. Interestingly, in a recently published scientific paper, Ott *et al.* (1996) reported that by comparing average respirable particulates concentrations in a tavern measured before and after prohibition of smoking, they found smoking contributed 77% of the total indoor respirable suspended particulates in the tavern. The other sources, such as cooking and resuspended dust, contributed 23%. This study demonstrated the usefulness of respirable suspended particulates as a marker for ETS.

6. Comment Summary: “You note (2-21) that ‘classifying an individual’s exposure to ETS on the basis of spousal smoking habits may result in misclassification.’ Yet all 30 studies that were used by the EPA are specifically based only on the habits of smoking spouses. Your conclusion (2-22) that misclassifications about exposure would understate exposure, seems truly without base. Especially in light of your assertions (2-27) that increasing numbers of smokers don’t smoke in their own homes.”

Response: Comments on misclassification of smoker status have been raised by other commenters as well, and the reader is referred to OEHHA responses to comments by Drs. Stuart Brody, LeVois and Layard, and others in Appendix B.

7. Comment Summary: “Three other studies you apparently don’t acknowledge are the study by Healthy Buildings (whose falsely maligned ex-utive (sic) has finally gotten cleared) and a study using personal environmental monitors (Phillips *et al.* Environment International, 1994). The latter, as reported in the London Sunday Telegraph (Dec. 18, 1994), had concluded that non-smokers were exposed “to the equivalent of 5 cigarettes a year.” An amount so negligible as to render ETS an ‘unlikely cause of lung cancer.’ (Or a

cause of anything else?) You've also refused to read the new study by William Butler (15) or (apparently) anything else that contradicts your conclusions or those of the EPA.”

Response: No reference was given on the studies done by Healthy Buildings nor by William Butler. The use of cigarette equivalent approach to compare ETS with active smoking is a complex issue and has been challenged by many researchers in the field. Furthermore, for certain carcinogens, Hammond *et al.* (1995) estimated that workplace exposure can lead to cigarette equivalent of over half pack per day.

A. Judson Wells

1. Comment Summary: The chapter does not discuss the relative effects of deposition on active and passive smoking. According to Pritchard et al (1988), about 70% of the tar in aged ETS evaporates into the gas phase. Apparently the lung has no clearance mechanism for vapor phase deposits. The ETS compounds most likely to become vapor phase deposits are those with molecular weights in the 100 to 200 range including quinolines, phenanthridene, nor nicotine, b-naphthyl amine, nitroso pyrolidine, nitroso nor nicotine and several others all of which have carcinogenic potential. Mainstream smoke, by contrast, consists mostly of large particles that deposit mostly in the mouth and larger airways where most are cleared to the mouth and swallowed.

Response: The purpose of the chapter is to summarize some of the commonly used methods for measuring ETS markers and biomarkers. This information is useful as ETS marker and biomarker results are often used to validate questionnaire and interview findings. We do not feel a detailed discussion of vapor and particulate phase of ETS constituents is warranted in this chapter.

2. Comment Summary: Recently, Drs. Perez-Stable, Wagenknecht, English and Wells have submitted a paper for publication that essentially doubles the amount of misclassification data available in the US EPA report. The new data show misclassification rates that are about the same as those US EPA used, thereby further strengthening US EPA's conclusion that smoker misclassification has only a minor effect on the relative risk of lung cancer from passive smoking.

Response: The paper is currently not published and has not been made available for OEHHA review.

Comment Summaries and Responses on Chapters 3, 4, and 5: Developmental Toxicity and Reproductive Effects

Philip Morris

Philip Morris USA, submitted by Richard Carchman, Scientific Affairs

1. Comment Summary: The commentator makes a number of general assertions regarding the section on low birthweight and ETS exposure:

- a) The criteria for causality are unclear
- b) Inadequate exposure assessment, biomarker limitations and smoker misclassification make the evaluation inadequate for hazard identification
- c) Many of the study findings lack statistical significance
- d) The description of the effect as “small in magnitude” is undefined
- e) The clinical significance of small birthweight decrement is unclear
- f) The power of the studies to detect small changes is questioned
- g) Many of the studies fail to adjust for confounders and fail to present detail (no list of confounders)
- h) The phrase “adequate control of confounding” in describing a study is undefined
- i) OEHHA accepts the US EPA approach to calculating attributable risk uncritically

Response: In regard to the criteria for causality, exposure assessment, biomarkers, misclassification error, clinical significance, statistical concerns, and confounding, these issues have been raised and considered previously. The description of the change in birthweight as “small in magnitude” is relatively straightforward when viewed as a proportion of total birthweight. Although many factors may be related to birthweight, their distribution by ETS exposure status must vary in order for them to confound an association of ETS and birthweight. Studies considered adequately controlled for confounding take into account the major risk factors which may have an impact on the determination of an association. Many of the major co-variables for birthweight are identified in Section 3.2.2 Human Studies of Fetal Growth and ETS Exposure. The approach used by US EPA to calculate attributable risk which we cited is based upon standard methodology which can be used for any disease which can be attributed to an etiological factor.

2. Comment Summary: The commentator makes a number of general assertions regarding the section on postnatal manifestations of ETS exposure (particularly SIDS):

- a) Data from studies with inadequate control for confounding were included. There are a broad array of other risk factors which include: social and environmental factors, infant characteristics, pregnancy characteristics, maternal characteristics.

- b) The SIDS definition is outdated (1970). According to the 1989 SIDS definition, a postmortem examination of the infant is required and this has not been done in many studies.
- c) There are uncertainties as to the cause(s) of SIDS (SIDS is actually a category of deaths).
- d) The commentator recounts risk factors and estimated deaths from SIDS generated by the SIDS Alliance.
- e) The OEHHA review of studies is not thorough, confounding has not been ruled out, and the causality has been questioned by many.
- f) The commentator raises questions concerning specific studies (see comments below).

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses. Both the definition cited in the document (Beckwith, 1970) and by the commentator (Zylke JW, Sudden Infant Death Syndrome: Resurgent research offers hope. JAMA 262(12):1565-6, 1989) require thorough postmortem examination of the infant. Regardless, the primary studies cited in the document in support of the finding of causality were conducted after 1989. Although the “cause” of SIDS is unknown (and is probably multifactorial), the study of risk factors is still vital for understanding the pathogenesis of the syndrome, and for identifying potentially modifiable factors that could allow the incidence of the syndrome to be lowered.

Comments/responses presented below present the concerns of the SIDS Alliance. We believe our review is thorough. Several studies, which carried the most weight in forming our conclusions, did have adequate control of confounding.

All studies, inevitably, have some limitations; such limitations were duly noted in the document. This does not diminish the fact that several studies, with different designs, different populations, and varying degrees of controlling for confounding, found remarkably similar relationships between ETS and SIDS risk. This makes the assertion that the relationship between ETS and SIDS is entirely due to uncontrolled confounding unlikely.

3. Comment Summary: In regard to Bergman and Wiesner (1976), the commentator notes the study’s failure to adjust for covariates, the possibility of recall bias, the absence of statistical significance, and the inconsistency of the finding only among mothers ≤ 25 years old.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

4. Comment Summary: In regard to McGlashan (1989), the commentator notes the absence of adjustment for covariates, the potential for other related factors to be creating the association responsible for the elevated OR reported for maternal smoking.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

5. Comment Summary: In regard to Mitchell *et al.*(1991), the commentator notes that the paper cannot be used to support claims of a causal relationship between ETS exposure and SIDS because in the multivariate analysis, any maternal smoking in the two weeks prior to interview had a statistically insignificant odds ratio.

Response: The study summary notes that the 95% confidence interval on the OR bordered unity (1.0-3.3). The discussion also notes that extensive overlapping between women smoking during and after pregnancy precluded any attempt to identify an independent relationship with ETS exposure.

6. Comment Summary: In regard to Nicholl and O’Cathain (1992), the commentator has concerns that the only factor controlled for was spousal smoking and that inconsistencies in the paper were dismissed, despite being called “problematic.”

Response: This issue has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses. The description of the study authors’ finding that maternal smoking was less important than partners’ smoking in infants ≥ 24 weeks of age as “problematic” is appropriate for this study.

7. Comment Summary: In regard to Schoendorf and Kiely (1992), the commentator has concerns regarding the accuracy of using self-reported data for estimating ETS exposure as well as the limits to the control for confounding variables. OEHHA also does not address the fact that inconsistent relationships were reported for black and white infants for smoking and other household members and the risk of SIDS.

Response: The potential for misclassification and confounding error are issues which have been raised and considered previously. The significance of the relationship in whites, but not blacks, has been noted in the document.

8. Comment Summary: In regard to Mitchell *et al.*(1993), the commentator notes the limits to the adjustment for confounders, the small study size, and the absence of a significant effect when the analysis was done of other smokers in the household.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses. Any limitations due to the size of the study may be borne out in an inability to detect statistically significant differences between study populations and SIDS risk.

9. Comment Summary: In regard to Mitchell *et al.*(1995), the commentator notes the lack of control for confounding and the inconsistency of the finding that there was higher risk for mothers who never smoked in the house relative to those who did.

Response: This issue has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses. As noted in the document, small sample size may have accounted for the inconsistency of the findings.

10. Comment Summary: In regard to Klonoff-Cohen *et al.*(1995), the commentator notes the wide confidence intervals, the small number of subjects, the potential for recall bias and the contribution of sleep position as a risk factor.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

11. Comment Summary: In regard to Blair *et al.*(1996), the commentator questions the exposure data which were based on parental reports of smoking habits, the potential for recall bias, and the lack of control for confounding

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

12. Comment Summary: Postnatal Manifestations (Cognition and Behavior). The commentator claims that the discussion of the epidemiological studies examining the association between active maternal smoking during pregnancy and cognition and behavior in children is not relevant to the discussion of postnatal ETS exposure of a child.

Response: These studies have been reviewed at the beginning of the section to provide a context within which to consider the results of the studies of ETS exposure.

13. Comment Summary: The commentator submitted a list of additional literature not cited in the Final Draft of Chapters 3 and 4. [The relevance to specific aspects of the chapters was not identified for many of the articles, although several references (especially those for Chapter 4) were used in support of some of the comments above.]

Response: Some of the articles referred to for Chapter 3 relate to confounding (psychological stress, maternal work during pregnancy, father's drinking) of the effects on birthweight and birth defects. Others are reviews of the relationship of passive or parental cigarette smoking on developmental and reproductive endpoints. The articles referred to for Chapter 4 included general reviews of the etiology of SIDS as well as specific aspects such as confounding (sleep position and child abuse). These studies were not considered to contribute substantial information beyond that already reported in the document and therefore were not summarized and included.

Nigel Brown for Philip Morris

1. Comment Summary: Birthweight. The commentator has several concerns that:
a) the apparent effect of ETS exposure may be due to confounding variables

- b) a small decrement in birthweight may not be a significant health risk
- c) the calculated health risk is based on a theoretical extrapolation not supported by direct observation
- d) active smoking can not be used to justify a shift in the birthweight curve by ETS
- e) the direct studies of low birthweight are compatible with no effect of ETS
- f) the relationships between self-reporting, biomarkers and exposure are poorly understood

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

2. Comment Summary: Spontaneous abortion. The commentator notes that there was inadequate control for confounding, the relationship is not consistent, and the paternal contribution to the risk is unknown, thus the conclusion that a causal relationship is suggested is overstated.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

3. Comment Summary: Congenital malformation. The commentator claims that the document's conclusions are too strong because of inconclusive/insufficient data.

Response: The document's conclusion was that it was not possible to determine whether there was an association, which is appropriate given the available data.

4. Comment Summary: Female and male reproductive toxicity. The commentator notes that "the Executive Summary and Draft Document reflect the available data wholly accurately in the field of female and male reproductive toxicity."

Response: The comment has been noted.

Bruce Kelman, Golder Associates, for Philip Morris

1. Comment Summary:

- a) "The agency failed to adequately define the process of evaluation which would be used in the Draft."
- b) "The process of determining causality which the Agency did identify is flawed."
- c) "The agency failed to follow its own process."
- d) "When the Agency made use of scientific literature, they incorrectly quoted results from the literature."
- e) "The Agency fails to critically evaluate the literature. At the simplest level, the Agency failed to determine whether the authors' conclusions are supported

by the data. At a more complex level, the Agency failed to evaluate the experimental and statistical design of studies.”

Response: These comments have been raised and considered in the comments/responses relating to Chapter 1. These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

2. Comment Summary: The animal literature does not include dose-response studies, mechanism studies, critical period studies and studies are inconsistent in their results.

Response: The animal literature contributes to the weight of evidence determination and is not the primary basis for any conclusions.

3. Comment Summary: The exposures in the Leichter study are more similar to MTS than ETS and are not confirmed by biomonitoring. The study was not designed to study ETS.

Response: We included animal studies with “tobacco smoke” exposure as indicated by the title of the section. We characterized a study as using “sidestream smoke” if the smoke came directly from the lit end of the cigarette. Lack of biomonitoring does not exclude the study from contributing to the weight of evidence. The design of the study includes comparison of control and sidestream groups and so is relevant to the document.

4. Comment Summary: The Witschi study was primarily a study of transdermal patches and not specifically designed to assess fetal weights.

Response: The study included comparison of control and SS groups and measures of fetal weight and thus is relevant to the document.

5. Comment Summary: The Rajini study combines the results from 2 different experiments.

Response: The methods for both studies are available for evaluation in the article. No apparent barrier to combining the data from the two studies was identified.

6. Comment Summary: The argument that litter size and fetal weight are reciprocal and that the fetal period is more susceptible to growth retardation may not apply to toxic exposures.

Response: These general principles of developmental biology and toxicology were introduced to help understand the inconsistency between two studies. They may not apply to every type of toxicant exposure, depending on its mechanism.

7. Comment Summary: In regard to epidemiological studies, conclusions should not be drawn from studies in which the sample size is too small to detect a statistically

significant difference in effect. The commentator also states that Cal/EPA has failed to define significance levels and power in the studies cited in the document.

Response: Sample size is among the aspects of study design which were evaluated in determining which studies were to be considered in drawing conclusions from the available studies. When presented in the original articles, relevant significance levels were included in the document. Study power is a detail rarely available from the original literature and its calculation and presentation for each of the many studies described is beyond the scope of the document. The power of a study is basically a moot issue if a study has statistically significant findings (the study was by definition large enough to detect a statistically significant difference). Knowing a study's power is most helpful in interpreting negative studies. In these cases it helps readers to decide if the study was large enough to detect a difference. Statistical significance is addressed in the Introduction.

8. Comment Summary: In regard to the fetal growth effect of ETS exposure, the commentator claims that the lack of statistical significance of the studies indicates there is no consistency of association.

Response: Consistency of association does not require statistical significance.

9. Comment Summary: The commentator claims that the statement in the 1997 draft that "[a]ll but one of the studies that examined mean birthweight have shown a decrement with ETS exposure, although some of the weight differences were small" rejects the use of statistics. The commentator asserts "that Cal/EPA inappropriately combined the results of several nonsignificant studies in an attempt to create a single significant study."

Response: Data pooling is not done only with "significant" studies (see any paper/text on meta-analysis) and can allow further classification or evaluation of the studies in the analysis.

10. Comment Summary: The commentator asserts that retrospective studies are weak for establishing causality and that the "majority of the studies used by Cal/EPA to support their claim were retrospective studies".

Response: While retrospective studies are limited by the potential for lack of control for the types of errors for which prospective studies can be controlled, they do have the ability to identify certain aspects of relationships which can be used in establishing causality.

11. Comment Summary: The commentator claims the studies used in the meta-analysis of fetal birthweight has a population too diverse to support a true meta-analysis and that there is inadequate detail in the text of the Final Draft to establish the quality of the meta-analysis. The statement regarding the meta-analysis (p. 3-23) "has not been supported by either a tabular rating or text in the final draft."

Response: The conclusions of the section on birthweight are not based on the findings of the meta-analysis; it was brought in to provide numerical context. Nonetheless, additional information concerning its generation has been added to the text of the birthweight section.

12. Comment Summary: Attributable risk. “No theoretical or mechanistic justification exists for using a cancer risk model for low birthweight.”

Response: The attributable risk calculation, which was originally described in terms of lung cancer and smoking (Levin ML. The occurrence of lung cancer in man. *Acta Unio Internat Contra Cancrum* 9:531-41, 1953; Levin ML and Bertell R. Simple estimation of population attributable risk from case-control studies. *Am J Epidemiol* 108:78-9, 1978) is generalizable to any disease which can be attributed to an etiological factor and does not require theoretical or mechanistic justification (Lilienfeld AM and Lilienfeld DE. *Foundations of Epidemiology*, 2nd edition, New York: Oxford University Press, 1980).

13. Comment Summary: “The draft does not convincingly demonstrate the biological plausibility of ETS as causing the purported effects [SIDS] at levels normally present in the breathing zone of the parent or infant” and “does not rule out bias and confounders with reasonable confidence.”

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses. Articles were presented that provide plausible mechanisms through which ETS could exert an effect. Regardless of the state of current knowledge regarding biological mechanisms, the finding from the epidemiological studies, which are strong and consistent, cannot be ignored.

14 Comment Summary: In regard to the Eskenazi *et al.* (1995) study, the commentator has concerns regarding the study authors’ claim of biological plausibility given the lower level of nicotine and carbon monoxide in ETS, the absence of a statistically significant effect when adjusted for gestational age, the appropriateness of serum cotinine levels in evaluating exposure, the accuracy of the analysis in using samples stored long after collection, and the observation of a dose-response only among mothers who were active smokers.

Response: The 1997 Final Draft did not address the authors’ claims regarding the issue of biological plausibility nor the issue of dose-response for this particular study. Eskenazi *et al.* did not examine a dose-response effect among only ETS-exposed, so it is not possible to say it is or is not present. Their multiple regression model would indicate a dose-response within cotinine levels commonly found among ETS-exposed women. The other concerns were noted in the study summary in the Draft.

15. Comment Summary: In regard to Rebagliato *et al.* (1995a), the commentator has concerns about the study's failure to identify the type and sources of biomarkers in studies used in support of their case for biological plausibility. Cal/EPA [OEHHHA] also gave no consideration to the issue of comparability of cotinine measures in saliva relative to measures in serum. The commentator also notes that the highest mean birthweight was observed in the second highest quintile group (1.2-1.7 ng/mL cotinine), which is higher than that reported for the lowest exposure group, and this was not reported in the 1997 Draft. The authors also did not address the possibility of recall and/or reporting bias.

Response: The study authors' contention of biological plausibility of low birthweight resulting from reduced fetal blood flow from ETS exposure is not addressed in the 1997 Draft. The issue of the appropriateness of salivary sampling in cotinine measurement has been addressed in Section 2.4.2 Biomarkers: Nicotine and Cotinine. In regard to the high birthweight in the second highest cotinine level quintile group, a statement with this information has been added to the document. This issue has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

16. Comment Summary: In regard to Haglund *et al.* (1995), the commentator claims "[i]t is inappropriate for Cal/EPA [OEHHHA] to use this study to support the claim that postnatal ETS may cause SIDS" because postnatal ETS exposure was not measured. "Cal/EPA [OEHHHA] gives no indication as to the purpose that this study may serve." It was also noted that the relative risk of 3.1 (reported as 3.5 in the 1997 Draft) for early SIDS resulted from a high rate during spring (4.9). Removal of the spring value from the calculation reduces the mean to 2.5, comparable to the late SIDS value. "Cal/EPA [OEHHHA] gives no indication as to the intention that this study may serve." The commentator also has concerns that it is inappropriate to use this study to support the claim that postnatal ETS exposure may cause SIDS because there is no explanation regarding the biological plausibility linking prenatal maternal smoking with postnatal ETS exposure and SIDS.

Response: This study was included because it is among those which attempted to examine the relationship between ETS exposure and SIDS (p.4-9). The 1997 Draft reports the authors' speculation that because the risk associated with maternal smoking did not rise in the winter, when indoor ventilation might be poorer, prenatal tobacco exposure might be more important than postnatal exposure. The limitations of the study were noted as well.

17. Comment Summary: In regard to Haddow *et al.* (1988), the commentator states that the study was not controlled for gestational age, although the 1997 Draft claims that the study was adequately controlled for confounding. Also mentioned were the limitations of using cotinine levels as an indicator of exposure over an extended period and the weakness of the dose-response observed in the study (non-linear). "Non-linearity cannot be used to suggest a relationship between cotinine and low birth weight unless some model has been tested to indicate that this is the case."

Response: The absence of controlling for gestational age limits the ability of the study to differentiate between an effect related to prematurity or growth retardation. Possible confounders which were not included have been mentioned in the study summary. The limitations of cotinine as a biomarker for ETS exposure have been addressed in other parts of the document. The model did not indicate non-linearity, rather, there was a mismatch in the comparison of the model estimate to the overall decrement.

18. Comment Summary: In regard to Mainous and Hueston (1994), the commentator questions the authors' contention of a threshold effect, citing the absence of significant difference in effect between exposed and unexposed groups. The commentator later states that this also shows that there is no true dose-response relationship. The study is also subject to recall bias and exposure is not quantitated.

Response: The noted effects on LBW and mean weight were significantly different from the comparison in the highest exposure group. The 1997 Draft Report summarizes the authors' claim of a threshold without comment and also notes the absence of a significant dose-response relationship. The other limitations have been noted in the document.

19. Comment Summary: In regard to Mitchell *et al.* (1995), the commentator claims the failure to control for confounding limits the Agency's ability to use it in establishing a causal relationship.

Response: This study had quite limited value in evaluating the weight-of-evidence classification for ETS exposure and SIDS, and thus the limitations of this single study did not weigh heavily in its consideration.

20. Comment Summary: The commentator asserts that the weight-of-evidence classification for the association between spontaneous abortion and ETS changed to "suggestive" with only the consideration of one new study, an abstract (Windham *et al.*, 1995b). The conclusions of the study are not supported by other studies, and the effect of confounders (like alcohol) have been ignored.

Response: The weight-of-evidence aspect of the document was considerably expanded to a more complete form between the March 1995 draft and the 1997 Final Report. Concerns regarding confounding have been considered in the evaluation of the evidence.

21. Comment Summary: Cognition and Behavior. The 1997 Draft should not have cited Eskenazi and Trupin (1995) in establishing a relationship between ETS exposure and postnatal childhood behavior because its authors' could not rule out uncontrolled confounding as responsible for the observed effect.

Response: This fact has been noted in the study summary. The study has been included because of its relevance to the body of literature examining the relationship of postnatal ETS exposure and effects on cognition and behavior in children.

22. Comment Summary: Cognitive Development. The commentator claims that five studies were described in the 1997 Draft as ‘well-controlled’, but the commentator considered them as inconclusive, inconsistent, and inadequately controlled. The commentator suggests that since the document states that “no conclusion regarding causality can be made on the basis of studies reviewed”, that a ‘suggestive’ categorization is inappropriate since a causal interpretation needs to be found credible.

Response: In regard to the description of the studies relating ETS exposure to cognitive development, only one was described as ‘well-controlled’. The others were described as ‘fairly well-controlled’. The limitations mentioned by the commentator have been described in the document and considered in the weight-of-evidence classification. Simply because an exposure/effect relationship cannot be concluded to be causal does not mean that a causal relationship cannot be considered credible.

23. Comment Summary: In establishing a causal association between ETS exposure and birthweight, the Agency does not give more weight to studies that can distinguish pre-and postnatal exposure from *in utero* exposure due to maternal active smoking.

Response: Of the biomarker studies, the Haddow *et al.*(1988) study provided the most convincing evidence of an effect on growth (or weight). The study population was limited to nonsmokers (1231 pregnancies). The summaries of all studies reviewed plainly state whether maternal active smokers or nonsmokers were examined; most studies were conducted among non-smokers and those are considered the highest quality. Post-natal exposure cannot affect growth *in utero* as reflected by birthweight.

24. Comment Summary: “[C]otinine levels cannot be accepted as a ‘gold standard’ for long-term exposure at the current time.” The commentator has concerns that studies utilizing cotinine levels for ETS exposure assessment are used to provide the ‘most-convincing evidence’ for endpoints such as fetal growth.

Response: The 1997 Final Draft describes the limitations to the use of cotinine levels in evaluating ETS exposure (Section 2.4.2 - Biomarkers: Nicotine and Cotinine). The study referred to as providing the ‘most-convincing evidence’ (Haddow *et al.*, 1988) was considered strong for its ability to evaluate the occurrence of low birthweight among ETS-exposed subjects, not for its ability to identify a dose-response relationship. Pregnancy studies do not typically involve long-term exposure, but rather exposure limited to pregnancy. The cotinine levels reported in Haddow *et al.*, were measured during the second trimester.

25. Comment Summary: In regard to Martinez *et al.*(1994), the commentator states that 1) the 34 gram birthweight decrement associated with paternal smoking may be erroneous because Table 2 (of the original study) does not specify which coding variable resulted in this decrement, and that maternal smoking of 20 cigarettes per day is associated with a decrement of 273 grams rather than 250 grams which is not credible because it is larger

than the effect associated with maternal smoking [sic]. 2) The balance of the variability for maternal smoking (96.3%) and for paternal smoking (99.5%) and a decrease in birthweight is unexplained by the authors, leaving the qualitative interpretation of the study unexplained. 3) Numerous confounders were not controlled for (maternal alcohol use during pregnancy, nutritional habits, prenatal care, workplace exposure). 4) The data concerning the frequency of cotinine detection in infants' cord blood correlation with paternal smoking is not presented in the paper and Cal/EPA does not discuss several observations in the study that infants of smoking and non-smoking fathers had low levels of cotinine.

Response: 1) The 34 g birthweight decrement noted by the commentator seems to be clearly associated with paternal smoking in the original study. While the decrement described for maternal smoking is for maternal smoking (and thus not comparable to itself) (the commentator may have misstated the intended comparison), the rounded value of 250g reported in the draft summary has been changed to 273g as reported in the original study, according to the commentator's suggestion. 2) While the degree of unexplained variability in this analysis is relatively high, most of the variability in studies of birthweight is unexplained. 3) These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.. 4) The issue of the correlation of cotinine levels and ETS exposure has been extensively covered in Section 2.4.2 (Biomarkers: Nicotine and Cotinine). Martinez *et al.* (1994) reported that cord blood cotinine was strongly correlated with the number of cigarettes smoked by the father. While there is the observation that some infants of smoking fathers in this study may have low levels of cotinine, it was accepted that the correlation between cord blood cotinine and paternal smoking was good.

26. Comment Summary: In regard to Mainous and Hueston (1994), the difference in birthweight of 84 g was between "high" and the "very low" exposure groups, rather than the "highest" and "unexposed" infants as described in the 1997 draft. Also the statistical significance of this difference was not presented, thus Cal/EPA is incorrect in stating this comparison.

Response: While the respondents to the questionnaire categorized themselves as "never" exposed to ETS, the study's authors suggested that semantic differences may have led respondents to categorize themselves this way in spite of low exposure, thus the authors considered this a "very low" exposure group. The study summary has been modified to more closely reflect the authors' interpretation. This finding was "statistically significant" as indicated by the confidence interval in Table 3.3.

27. Comment Summary: In regard to Chen and Pettiti (1995), the 1997 Draft reports that the subjects were interviewed fairly soon after delivery (mean of 8 months), although "[t]here is no indication in the article when the interviews actually took place."

Response: The Results section of the study indicates that the "subjects were interviewed a mean of 33.1 weeks after delivery."

28. Comment Summary: In regard to Roquer *et al.*(1995), the assignment of a range of 1 to 9 cigarettes per day to a group described as smoking less than 10 cigarettes per day is inaccurate because it excludes the possibility that no cigarettes were smoked at all by this group. Also the assertion that the p-value associated with relationship of ETS exposure and reduction of 1 cm length of less than 0.001 should be “p=0.000” as reported in the article, which is not credible.

The commentator notes that the passively exposed group did not differ significantly from the nonexposed or highly exposed group.

Response: Since the group members smoking less than 10 cigarettes per day were in the ‘smoker’ category, it would be inaccurate to include zero cigarettes in this category (they would be included in non-smokers). In regard to the p-values reported in the study, the reported value of p=0.000 was interpreted to mean a value whose first significant figure is in the fourth decimal place which would include $p < 0.001$. The repetition of this value in the paper indicates it is a convention, and thus is not a typographical error. However, it may refer to the ANOVA, which included smokers, therefore, we calculated a confidence interval and will substitute it in the study summary (-1.8, -0.2).

29. Comment Summary: Milerad *et al.*(1994). The commentator contends that the study was conducted on 24 consecutive cases, rather than the 16 referred to in the 1997 Draft. Sixteen of the 24 were classified as SIDS cases. The comment also provides additional findings of the study including that:

- a) 7 SIDS cases as well as 5 non-SIDS cases were moderately exposed and 2 SIDS and 2 non-SIDS cases were heavily exposed (therefore 7 of 8 non-SIDS cases had levels similar to SIDS cases).
- b) Two cases with high nicotine and moderate cotinine levels were assumed to have been contaminated and that two cases were autopsied with an autopsy assistant who was a heavy smoker.
- c) 7 of the 16 SIDS infants and 1 of the 8 non-SIDS infants were not significantly exposed around the time of death.
- d) It is unknown whether the 16 of 24 returned questionnaires were SIDS or non-SIDS subjects.
- e) The commentator surmises that only 16 of the infants would have detectable cotinine levels at postmortem since 8 subjects were measured as having 1.5 (or 2 ng/mL) at postmortem. To obtain 71% detectable level, 17 infants would have to have detectable levels.
- f) Table I indicates 8 cases showed cotinine levels less than 2.0 ng/mL whereas the text refers to these cases at less than 1.5 ng/mL. No information on the smoking practices of family members is presented.
- g) It is unclear whether the 2 cases in which the 1997 Draft claims contamination was suggested are SIDS or non-SIDS cases.
- h) The 1997 Draft claim that “6 of 8 infants whose percentage disclosed other contributing causes of death had cotinine concentrations greater than 10

ng/mL” is incorrect; Table 1 of the study shows only 5 non-SIDS infants with these levels.

The commentator also reviews the limitations of using cotinine levels in evaluating long-term exposure.

The commentator questions the use of postmortem pericardial fluid as a ‘surrogate’ medium for serum and plasma.

Recall bias may be a problem since the year the questionnaires were submitted is unknown.

Response: Given the limited value of this study in establishing a relationship between ETS exposure and SIDS risks, many of the details of the study identified by the commentator were not included in the summary. The issue of cotinine levels as an indicator of ETS exposure has been extensively covered in Section 2.4.2 Biomarkers: Nicotine and Cotinine. This issue has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

30. Comment Summary: In regard to Mitchell *et al.* (1995), the commentator states that the original article shows the number of women who never smoked in the house was 6 whereas the number of controls in that category was 12. The 1997 Draft reported that n=18. The commentator also states that the study is subject to recall bias because of the length of time that passed between the date of death and the postal interview. The commentator also states the authors’ claim that the increased risk of SIDS produced by smoking may be primarily due to the effect of smoking on the fetus *in utero*, and therefore there is not an association of ETS exposure to SIDS.

Response: The *n* value reported in the sentence cited in the comment refers to the total of both cases and controls. While not specifically mentioned for this study, recall bias is a potential source of error which has been generally considered in evaluating the literature relating SIDS risk to ETS exposure. The authors’ statement regarding the possibility that the observed effect may be due to the effect of smoking on the fetus *in utero* is questioned because of the size of the group of women driving this conclusion is very small and the smoking habits of other family members were not accounted for.

31. Comment Summary: The commentator states that no statistical analysis was performed on the data reported for the Comstock and Lundin (1967) study.

Response: Although the authors presented no statistical testing of the differences in the adjusted rates, a crude odds ratio and 95% confidence interval for the association of neonatal death and paternal smoking were calculated (OR=1.45, 95% CI=0.9-2.4) because the adjusted rates presented by the authors were very similar to the crude rates.

32. Comment Summary: The commentator reviews the findings of the Fortier *et al.*(1994) study, stating they are either weak or non-existent.

Response: The findings described in the comment were reported in the 1997 Draft.

33. Comment Summary: In regard to Eskenazi *et al.* (1995), the commentator states the p-value of 0.28 was used when discussing the association between decreased birthweight in infants of exposed nonsmokers and unexposed infants and this value has been accepted by Cal/EPA. Furthermore the results of the study are insignificant and show no association. The authors' claim of biological plausibility because two major component of MTS and ETS are carbon monoxide and nicotine are not supported. The commentator states that the trend of decreasing birthweight was only observed among smokers, not in the ETS exposed. The comments suggests that the study is questionable given the use of old serum samples for cotinine analysis.

Response: The decrement in birthweight in infants of exposed nonsmokers and unexposed infants was not reported to be significant, but the study was considered to be one of many which do show a decrement in birthweight (see Discussion). The authors' claim of biological plausibility was not reported in the study summary. The trend observed regarding smokers and decreased birthweight was not reported in the document in an effort to limit the presentation of data regarding the effects of active smoking, but, as noted in a previous comment regarding this study, the trend by cotinine level included both smokers and ETS exposed groups. The appropriateness of using old samples for cotinine analysis was addressed in the document.

34. Comment Summary: In regard to Eskenazi and Trupin (1995), the commentator claims the study showed that children whose mothers are exposed to ETS during pregnancy did not have behavioral test scores that differed significantly from scores of children with no smoking exposure even after adjustment for confounders. Furthermore, this study showed no evidence for a dose-response relationship.

Response: The lack of statistical significance for the observed elevation for “active” behavior among children whose mothers were exposed to ETS during pregnancy (OR=1.5) has been noted in the document. The lack of a dose-response relationship has also been addressed in the document.

35. Comment Summary: In regard to Mathai *et al.*(1990), the commentator states that the study cannot be used to assess the birthweight effects of ETS because the results from multiple regressions include active smoking as a factor.

Response: Mathai *et al.*(1990) did not include active smoking in their analysis of ETS exposure and birthweight in the part of the study using women identified as non-smokers who lived with smokers. Only in the part of the study in which cotinine analysis was correlated to birthweight was active smoking included in the analysis.

36. Comment Summary: In regard to Rebagliato (1995b), the commentator claims the 1997 Draft discussion of this paper is misleading because it did not discuss the relationship of the significant cotinine levels to fetal birthweight; this was discussed in Rebagliato *et al.*(1995a).

Response: The discussion of cotinine levels and the results for the highest quintile group have been presented in the Table. Omission of the distinction between the two studies (1995a and 1995b) has been corrected in the document.

37. Comment Summary: In regard to Zhang and Ratcliffe (1993), the commentator claims the dose-response data are inconsistent, with greater weight decrements observed among those smoking up to 19 cigarettes per day than among those smoking more than 20 cigarettes per day.

Response: The study summary has been modified and now refers to the relationship as a non-linear trend rather than a dose-response. The detail referred to by the commentator is included in the summary.

38. Comment Summary: In regard to Haddow *et al.*(1988), the commentator claims a strong dose-response would be expected to be found if this were a strong study.

Response: Numerous factors other than the dose-response contribute to the strength of a study. The model with cotinine level as a continuous variable (up to 10 ng/mL to indicate ETS exposure) did find a significant coefficient as indicated in the study summary ($p=0.04$) and Table 3.4.

39. Comment Summary: In regard to Borlee *et al.*(1977), the commentator claims the study has little relevance to ETS because it was primarily an investigation of maternal smoking. It was not considered one of the highest quality studies as noted in the discussion section.

Response: Regardless of the primary intention of the study, it contains relevant information regarding the association between paternal smoking and birthweight (adjusted for malformation, prematurity and maternal tobacco use).

40. Comment Summary: In regard to Yerushalmy (1971), the commentator claims that paradoxical observations (other than the finding of increased LBW infants associated with paternal smoking) including higher neonatal mortality and risk of congenital anomalies for low-birthweight infants from non-smoking mothers related to distributional differences in birthweight are not experimentally supported.

Response: These findings were not included in the study summary. The document notes that no raw data were presented for estimation of an effect measure or confidence interval.

41. Comment Summary: Critique of Agency approach to comments. Inadequacies were identified in several of the responses to comments from the first comment period:

- a) The responses describing the reasons for the inclusion of active smoking data in the document is unacceptable because “acknowledging differences without discussing qualitative and quantitative differences is scientifically unacceptable.”
- b) A weight of evidence approach was identified in the response regarding the relationship of birthweight decrements to ETS exposure, although “the Agency fails to adequately define criteria to be used in the ‘weight of evidence’ approach.”
- c) The Agency fails to identify exactly what changes were suggested by Gio Batta Gori, thus obscuring what may be a better approach to the evaluation.
- d) The term “causal relationship between” should be replaced by “independent risk factor for” to be more scientifically correct since the term causal has not been defined in the document.

Response: Emphasis has been made throughout the document as well as in many comments/responses of the role of the inclusion of data from active smoking. These data have not formed the basis of any conclusions regarding the health effect of ETS. The issue of weight of evidence has also been carefully described both in the document itself (Section 1.4) and in the response to several comments (see above). The extensive nature of many of the comments required that comment summaries be made. Effort was made to capture any substantive issues captured by the commentator which would result in a positive contribution to its content. We feel that the terms for causality have been adequately defined in the document.

The Tobacco Institute

The Tobacco Institute, submitted by Clausen Ely of Covington and Burling, attorneys

1. Comment Summary: The commentator summarizes the concerns regarding the evidence of a relationship between low birthweight and ETS exposure, citing the lack of statistical significance in a number of studies, the “weak” association, lack of dose-response, failure to consider misclassification of active smoking status, failure to take confounders into account, the questionable health impact of the effect, the inadequacy of animal studies, and the degree of effect relative to active smoking.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

2. Comment Summary: OEHHA failed “to recognize or discuss the OEHHA Science Advisory Board Developmental and Reproductive Toxicant (DART) Identification Committee’s decision, at its meeting on May 12, 1995, not to list ETS as a reproductive toxicant based on the Committee’s determination that the available information failed to

satisfy the Proposition 65 requirement for clearly showing through scientifically valid testing according to generally accepted principles that ETS exposure causes an adverse effect on fetal growth.” Some Committee members’ statements were noted. OEHHA has an obligation to consider and respond to the issues raised by its own DART Committee.

Response: The document entitled *Developmental and Reproductive Effects of Exposure to ETS* (which appears as chapters 3, 4 and 5 in the current assessment) served as a hazard identification document for the Developmental and Reproductive Toxicant (DART) Identification Committee’s May 1995 consideration of ETS as a developmental and reproductive toxicant under Proposition 65. When the Committee met in May 1995, seven members of the eight member committee were present to consider and discuss the evidence on ETS. Four of the seven members present felt that ETS had been clearly shown to cause developmental toxicity based on decreased birthweight due to prenatal exposures to ETS. Under the new SAB regulations (22 CCR Section 12302(f)), a majority of appointed members (in this case, five) is required for the committee to take action, so ETS was not listed as a developmental toxicant under Proposition 65. The Committee discussed whether ETS had been clearly shown to cause sudden infant death syndrome (SIDS) based on a combination of prenatal and postnatal exposures. A finding was not made due to the uncertainty as to whether or not postnatal exposures could be considered in making a finding of developmental harm. At a meeting held in December 1996, the Committee expressed an interest in revisiting the question of listing ETS as a developmental toxicant on the basis of prenatal exposure. Because the details of this process are not scientific/technical in nature, they were not included in the document.

3. Comment Summary: OEHHA has failed to consider the weaknesses of the published studies regarding the association of SIDS risk with ETS exposure (inconsistent results, weak associations, failure to distinguish postnatal maternal smoking from maternal smoking before and during pregnancy, inadequate adjustment for confounders, and failure to validate maternal smoking status). Specific limitations of the Klonoff-Cohen study are also reported (wide confidence intervals, potential recall bias, illogical finding of greater risk for paternal smoking than for maternal, and no finding of a relationship between SIDS risk and sleep position). The Blair *et al.* study is similarly criticized and it is noted that it fails to adjust for maternal smoking during pregnancy. Mitchell *et al.* (1993) is criticized for its failure to show a paternal smoking effect.

Response: In the draft document, we have extensively considered study weaknesses in their evaluation. The issues concerning the Klonoff-Cohen *et al.*, Blair *et al.*, and Mitchell *et al.* studies have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

Gio B. Gori, Health Policy Center, for The Tobacco Institute (written and oral comments)

1. Comment Summary: Oral Comments. The commentator states that the literature on SIDS and ETS is contradictory and this should be the conclusion of the weight of

evidence classification. An editorial in the British Medical Journal is also cited which remarks that the Blair *et al.* study is inadequate to ascertain the relative contribution of pre- or postnatal exposure to tobacco smoke to SIDS risk. Blair *et al.* (and likewise Klonoff-Cohen) do not report risk due to maternal postnatal smoking after adjustment for maternal smoking during pregnancy.

Response: On the contrary, the literature is remarkably consistent. Both the Blair *et al.* and the Klonoff-Cohen *et al.* studies present analyses which control for maternal smoking during pregnancy. This issue has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

2. Comment Summary: Written Comments. Dose-response comparison with active smoking; confounding; clinical significance of low birthweight; misclassification is not mentioned in studies.

Response: The issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

Raphael Witorsch, Virginia Commonwealth University, for The Tobacco Institute

1. Comment Summary: The commentator critiques the studies used in the evaluation of low birthweight (citing smoker misclassification, recall bias, inadequate sample size, and confounding) and provides an independent analysis of the studies [also published in Witorsch RJ, Witorsch P (1996) *Indoor Build Environ* 5:219-231]. Concerns were also stated that the presented meta-analysis is not peer reviewed and that the available studies are unsuitable for meta-analysis.

Response: The issues of misclassification, recall bias, the limitations of sample size, have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.. The conclusions of the section on birthweight are not based on the findings of the meta-analysis; it was brought in to provide numerical context. Nonetheless, additional information concerning its generation has been added to the text of the birthweight section.

RJ Reynolds

RJ Reynolds Tobacco Company general comments

1. Comment Summary: The commentator provides an overview of those comments made by James Swauger of the RJ Reynolds Tobacco Company relating to the inadequacy of the published literature in establishing developmental toxicity (inconsistency, confounding, misclassification bias, recall bias, absence of quantitative measures of ETS exposure, absence of dose-response and limitations to animal studies).

Response: See response to specific comments below.

2. Comment Summary: Reprints of several published studies were submitted in support of the comments made including a review of the role of thermal stress/sleep position in SIDS (Sawczenko and Fleming, *Sleep* 19:S267-S270, 1996), a review of reproduction and smoking (Ravensholt *et al. Am J Obstet Gynec*, 96:267-81, 1966), a study of the effect of parental smoking and industrial pollution and its effect on birthweight (Rantakallio *et al. Indoor Air Quality*, Kasuga, ed., Springer-Verlag, 1990, pp.219-225), a review of the statistical considerations in the evaluation of epidemiological evidence (Yerushalmy. *Tobacco and Health*, James and Rosenthal, eds., Charles C. Thomas: Springfield, Ill. 1962, pp.208-230), a study of the effect of paternal smoking on fetuses (Kikuchi and Takahashi, *Int Arch Occup Environ Health Suppl* 0(0):272-277, 1990), and a Russian article on the birthweight, lactation, cotinine effect of exposure to passive smoke (Drózd *et al. Gin Pol* 59:528-533, 1988).

Response: These studies were not considered to contribute substantial information beyond that already reported in the document and therefore were not summarized and included.

RJ Reynolds Tobacco Company, submitted by Mary Ward

1. Comment Summary: “It is inappropriate to predict or characterize the potential activity of ETS based on the activity of any single constituent or group of constituents.” “Due to differences between mainstream smoke and ETS, inferring ETS health effects based upon mainstream smoke data is not appropriate”.

Response: The issue of ETS versus mainstream smoke has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

2. Comment Summary: The commentator reviews generally the issues of exposure timing, dose quantitation, misclassification, and confounders.

Response: See the responses to specific comments below.

3. Comment Summary: Birthweight. The commentator makes statements regarding general issues such as confounding, paternal smoking as a surrogate for ETS exposure, recall bias and the clinical relevance of the endpoint.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses. Some concerns regarding specific studies have been addressed below.

4. Comment Summary: In regard to Borlee *et al.*(1978), the commentator claims the study is limited by the “uniqueness” of the sample (malformed children), lack of

adjustment for confounders, the use of paternal smoking as a surrogate for ETS exposure, and the potential for recall bias.

Response: While the study did include malformed children in their analyses, the sample population did not consist exclusively of this subset. The 1997 Draft notes that this may restrict the generalizability of the results. The other issues have either been noted and considered in the Draft summary or addressed in other locations.

5. Comment Summary: In regard to Rubin *et al.*(1986), the commentator states that no data are provided by the authors regarding the number of nonsmoking females exposed to ETS, and thus control for maternal smoking cannot be done adequately. Other reviewers have suggested that bias and confounding (especially maternal height) could account for much of the observed association.

Response: The fact that maternal and paternal smoking were examined as variables in the regression analysis has been noted in the document. The document also notes that while the observed decrement was adjusted for many variables, maternal height and weight were not among them.

6. Comment Summary: In regard to Martin and Bracken (1986), the commentator states that the loss of a substantial percentage of the original study population could result in selection bias. Birthweight measurement is also subject to confounding.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

7. Comment Summary: In regard to Haddow *et al.*(1986), the commentator questions the appropriateness of the serum samples for cotinine analysis as well as the correlation to ETS exposure. Also the failure to account for confounding undermines the conclusions drawn in the study.

Response: The use and limitations of cotinine as a biomarker for ETS exposure have been considered in Section 2.4.2 Biomarkers: Nicotine and Cotinine. The limits of the authors' consideration of confounding has been addressed in the document with the conclusion that there is little evidence that important confounders were excluded.

8. Comment Summary: In regard to Campbell *et al.*(1988), the commentator cites confounding, poor exposure assessment, and recall bias as limitations to the utility of the study.

Response: These issues have been considered in the evaluation of the study.

9. Comment Summary: In regard to Martinez *et al.*(1994), the commentator cites confounding, the absence of exposure data (questioning the relatedness of cotinine levels to ETS exposure), and the potential for recall bias as limitations to the utility of the study.

Response: This study adjusted its regression analysis for 6 potential confounders although, as noted in the document, they did not include alcohol consumption and the use of smoking habits after delivery as representative of smoking during pregnancy. Cotinine as a biomarker for ETS exposure is extensively addressed in Section 2.4.2 Biomarkers: Nicotine and Cotinine.

10. Comment Summary: In regard to Mainous and Hueston (1994), the commentator states that no information was provided regarding the sample size of the exposure groups and that numerous confounding variables were not considered.

Response: While the raw numbers were not presented in the document summary or Table 3.3, close approximations to the size of each group can be made based on total sample population size presented and the percentage of the population represented by each subgroup. The commentator is referred to the original study for the exact size of each subgroup. The limitations to the consideration of confounding were noted in the Draft summary.

11. Comment Summary: In regard to Rebagliato *et al.* (1995), the commentator states that confounding, the absence of exposure data, and the lack of internal consistency in the data set undermine the conclusions.

Response: The limitations on the adjustment for confounding were noted in the Draft summary. This study had one of the most detailed exposure ascertainment, with questions about multiple sources of ETS as well as cotinine. The inconsistency of the results by source of exposure and the absence of a significant dose trend have also been noted in the Draft summary.

12. Comment Summary: In regard to Roquer *et al.* (1995), the commentator states the study is subject to confounding and there are no exposure data.

Response: The limitations from the lack of adjustment for confounders are noted in the document. Self-reported exposure data, which has limitations, was considered adequate to establish an exposed and unexposed population.

13. Comment Summary: In regard to Milerad *et al.* (1994), the commentator states that the study design precludes the possibility of distinguishing between potential effects related to active maternal smoking during pregnancy and postnatal ETS exposure. The commentator also questions the validity of using cotinine levels to evaluate ETS exposure.

Response: The commentator's statement regarding the study design is accurate. The utility and limitations of using cotinine levels for evaluating ETS exposure is addressed in Section 2.4.2 Biomarkers: Nicotine and Cotinine.

14. Comment Summary: In regard to Haglund *et al.* (1995), the commentator states that the methodology employed does not permit the examination of the relationship of postnatal ETS exposure and SIDS because the study examined the relationship of maternal smoking behavior and SIDS.

Response: As stated in the document, this study was included only because its authors felt that it had implications for the issue of pre- versus postnatal exposure.

15. Comment Summary: In regard to Mitchell *et al.* (1995), the commentator has concerns that because the highest increase in risk was associated when no smoking was reported to occur in the house (OR=5.07, CI=1.5-15.41), it is impossible to separate potential effects related to maternal active smoking during pregnancy and the potential effects related to postnatal ETS exposure. The commentator also notes the absence of a dose-response relationship, the potential for misclassification error, recall bias, selection bias, and the failure to adjust for certain confounders.

Response: The sources of error identified by the commentator have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

16. Comment Summary: In regard to Klonoff-Cohen *et al.* (1995), the commentator states concerns about confounding and recall bias.

Response: This issue has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

17. Comment Summary: In regard to Blair *et al.* (1996), the commentator has concerns regarding the adequacy of the control for potential confounders and the potential for recall bias.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

18. Comment Summary: Animal studies are not appropriate because they do not use ETS exposure. They are inconsistent.

Response: The exposure in all studies is appropriately described; relevance of animal studies is taken into account in weight of evidence determinations. The inconsistency between the two studies described can be attributed to the differences in timing of exposure as described in the text.

William Butler, Environmental Risk Analysis, for RJ Reynolds (oral comments)

Comment Summary: The comments made here addressed the association of ETS exposure and SIDS. The commentator contends “that ETS cannot be concluded to be a

cause of any of these health conditions; that interventions, even if based on good intentions, can indeed have negative impacts...; that the incorrect impression of an exclusive attribution, as would currently be derived from the CalEPA calculations, incorrectly attributes all of these events exclusively to ETS;...that specifically for SIDS – although I have no challenge with the algebraic calculations – such a strong, strong conclusion I do not think can be made without a more thorough review of all the available evidence, not just 11 case-control studies. And finally, it's necessary to calculate attributable risks for the other causes so as to put the other risk factors and causes – so as to put in perspective the relative potential contribution of ETS.”

Response: In regard to the attribution of SIDS deaths to ETS, please see the response to comments below (Mueksch, SIDS Alliance). Attributable risk is an accepted epidemiological tool which estimates the potential impact on public health of a particular exposure. Nonetheless, caveats have been added to the ETS draft regarding the attributable risk calculation. This is one of a set of comments on attributable risk; for further response to Dr. Butler's comments, see the comments/responses for Chapter 1 (Introduction).

Others

Otto J. Mueksch

Comment Summary: The commentator provided a copy of a letter from the Director of National Public Affairs of the SIDS Alliance to the Executive Director of ASH (Action on Smoking and Health) suggesting that published figures on smoking-related SIDS deaths are speculative and ungrounded in actual experimentation. This letter also asserts that although passive smoke exposure is a risk factor for SIDS, no direct causal relationship has been established and cautions that “we must refrain from making smoke exposure appear to be linked to *all* SIDS deaths.”

Response: The recent epidemiological studies have demonstrated that postnatal ETS exposure is an independent risk factor for SIDS. The SIDS Alliance has also recognized postnatal ETS as a risk factor and has cautioned that parents should “stop smoking around the baby” to reduce the risk (information on SIDS Alliance available at <http://www.cyfc.umn.edu/Children/sids.html>). While the ETS document identifies SIDS as causally associated with ETS exposure, it does not suggest that ETS exposure is responsible for all SIDS deaths (see also the attributable risk calculation). The figures presented in the document regarding SIDS deaths attributable to ETS exposure were produced from published estimates of SIDS risk resulting from household ETS exposure (Klonoff-Cohen *et al.*, 1995) and estimates of children exposed to household ETS (Pierce *et al.*, 1994). These estimates can thus be considered to result from “actual experimentation”. No single study can establish causation; a consensus grows as evidence accumulates. We feel that enough evidence has accrued to warrant our conclusions.

Marty Ronhovdee

Comment Summary: The commentator also quotes the letter from the SIDS Alliance to ASH (see Mueksch comment above) regarding causal relationships of ETS exposure to SIDS.

Response: See O. Mueksch comment/response above.

Linda Stewart

Comment Summary: Regarding the relationship of risk of low birthweight offspring to ETS exposure, the commentator contends that the relevant studies had disqualifying flaws including: failure to adjust for confounding (maternal height and weight, socio-economics, maternal working status, diet), absence of a dose-response relationship, failure to report statistical significance, and contradictory data between and within the studies [commentator provided no specific examples]. The commentator also contends that four studies did not show a decrement in mean birthweight (Underwood *et al.*, MacArthur and Knox, Yerulshalmy, Mathai *et al.*)

Response: OEHHA stands behind the description of these study findings in the document. These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

Jay Schrand

1. Comment Summary: The commentator provided a reprint of a paper he authored (Schrand JR, Is sleep apnea a predisposing factor for tobacco use? *Medical Hypothesis* 1996;47:443-8). The commentator contends that “genetic predisposition to sleep apnea and any other prior exposure to hypoxia by tobacco users is likely to be a confounding factor that has not been taken into account in any of the studies of purported childhood or spousal illnesses causally related to tobacco use or environmental tobacco smoke.” The commentator also claims the OEHHA report has also not taken selection and occupational factors into account. Endpoints of concern included fetal growth/low birth weight and SIDS.

Response: The commentator’s concerns regarding genetic predisposition to sleep apnea as a confounding factor has been addressed at another location in these comments/responses.

2. Comment Summary: The commentator notes that animals cannot choose/avoid ETS exposure and so differ from humans.

Response: This is a limitation of animal models that is not unique to ETS. It is offset by lack of confounding with factors that may be associated with choosing exposure, and by the ability to conduct controlled dose-response studies.

Carol Thompson, Smokers’ Rights Action Group

1. Comment Summary: Fetal growth. The commentator states that the claimed effect of maternal smoking during pregnancy on birthweight may be confounded by socioeconomic factors and *Helicobacter pylori* infection [references cited]. These factors were also noted for postnatal physical development.

Response: The evidence for an effect of maternal smoking is not detailed in this document, but it has been clearly shown in numerous studies and is accepted by medical experts.

2. Comment Summary: Spontaneous abortion and perinatal mortality. The commentator has concerns that physical activity and violence are important confounders which have not been adjusted for in evaluating the relationship of ETS exposure and spontaneous abortion [references cited]. In regard to perinatal mortality, the commentator cites another major cause of poor perinatal outcome is chorioamnionitis. [reference additions suggested].

Response: The document notes that at a minimum, maternal age, prior history of pregnancy loss, and socioeconomic status should be considered as potential confounders. The relative contribution of these other confounders has not been established, but their distribution by ETS exposure status must vary in order them to confound the association. It is not clear why this would be so with these particular factors.

3. Comment Summary: Congenital malformations. The commentator contends that valid study results require consideration of the adequacy of vitamin E during pregnancy in the prevention of CNS/neural tube defects.

Response: The document states in its discussion of the data regarding ETS exposure and congenital malformations that because of the relative dearth of information on causes of malformation, it is difficult to determine whether confounding variables have been adequately controlled.

4. Comment Summary: Postnatal manifestations (SIDS). The commentator suggests that sleep position is the more significant risk factor for SIDS.

Response: There are several risk factors for SIDS. Sleep position does appear to be an important risk factor; so does ETS exposure. Many of the studies cited found ETS to be a risk factor for SIDS independent of sleep position. Sleep position is a covariate which had been controlled for in several of the studies relating ETS exposure to SIDS risk (Blair *et al.*, 1996; Klonoff-Cohen *et al.*, 1995; Mitchell *et al.*, 1993). With this adjustment, significant risk is still associated with ETS exposure.

5. Comment Summary: Reproductive effects. Covariates related to sexual practices are inadequately considered in the claims of an effect of active smoking on fertility and its inclusion should have been a requirement for considering any study. The commentator also claims the evidence cited in the 1997 Final Draft that tobacco smoke is anti-

estrogenic is old [studies from 1982-1990 are cited] and that there is better, more recent work.

Response: The anti-estrogenic potential of ETS is an area in which OEHHA will remain interested in the future and the submission of any specific contributions to the recent literature would be well-received.

6. Comment: Cognition and Behavior in Children. “Those who are not just culturally biased but explicitly hostile members of an aggressor subculture should not even attempt to pass off their judgments as science. We have never seen any studies treating smokers and smokers’ children as daily victims of hate propaganda and attempted cultural genocide by anti-smoking demagogues, the government and their media collaborators. ‘Controlling for social class’ does not address this issue. Thus they are in a state of complete denial of the harm they are wantonly inflicting on others.”

Response: Consideration of this aspect of the development of a relationship between ETS exposure and effects on cognition and behavior in children is outside of the scope of this document.

A. Judson Wells

Comment Summary: “In Chapter 3 in the tables on low birth weight I saw no reference to the very fine paper by English *et al.*, Am J Public Health 1994;84:1439-1443.”

Response: The study cited is an examination of racial differences in serum cotinine levels among pregnant women smokers and the relationship to birthweight. The primary findings of the study are that black women had higher cotinine levels than white women after controlling for cigarette dose and confounding variables. No racial differences were found between black and white women with respect to birthweight decrements per ng/mL cotinine, suggesting that cigarette smoke may have a greater effect in black women compared to white women. While interesting, this particular study examines women who actively smoked during pregnancy and does not contribute significantly to the body of literature relating ETS exposure to birthweight decrements, and was thus not included in the document.

Comment Summaries and Responses on Chapter 6: Respiratory Health Effects

Philip Morris

Philip Morris USA, submitted by Richard Carchman, Scientific Affairs

1. Comment Summary: “OEHHA has omitted a large amount of relevant literature. Additional papers are referenced in Attachments to this Section of the Philip Morris Comment on OEHHA’s final draft.”

Response: Most of the papers referenced in Attachments A and B are actually already included in the OEHHA draft, despite the commenter’s implication to the contrary. A number of the papers included by the commenter are not relevant, and others are discussed below.

2. Comment Summary: “It is unclear how OEHHA moves from the position that ETS exposure may exacerbate (adult) asthma [p. ES-6] to the position that there is “suggestive” evidence for a causal relationship[Table ES-1]...What criteria or standards must be met for there to be ‘suggestive evidence’?”

Response: OEHHA staff agree with the commenter that, based on the current state of the science, it is probably premature to state that there is suggestive evidence of a causal relationship between ETS exposure and exacerbation of adult asthma, as stated in Table ES-1. Therefore, this condition will be deleted from Table ES-1.

3. Comment Summary: The commenter does not agree with the statement that “Household ETS exposure may affect severity of asthma in adults as well as children,” (p. 6-6) “[T]here are a number of other epidemiologic studies in the scientific literature that provide data on adult asthma and reported ETS exposures; taken as a whole, these studies report equivocal conclusions on this issue.” These studies are listed in Attachment A. “In the interests of sound science, OEHHA should consider all of the available studies, rather than selecting one[i.e., Jindal *et al.* 1994]. Were it to do so, it should reach the conclusion that the epidemiologic data do not clearly support claims that adult asthma is associated with ETS exposure.” The Jindal *et al.* report is subject to several other limitations beyond those noted in the OEHHA report.

Response: The commenter has either misunderstood or mischaracterized the quoted statement from the OEHHA document, which states, “Household ETS exposure may affect severity of asthma in adults as well as children.” This refers to ETS exposure as a factor potentially affecting the severity of asthma in adults who already have this condition. It does not mean that ETS exposure necessarily causes adult asthma in people previously free of this condition.

There are few studies of morbidity of adults with asthma in relation to repeated exposure to ETS. Despite its limitations, most of which are noted in the OEHHA document, the report by Jindal *et al.* (1994) does suggest that regular ETS exposure may affect asthma control in adults. As the commenter notes, this investigation undertaken in India may be of limited applicability in California. However, the other studies noted in the commenter's Attachment A do not necessarily shed additional light on this subject – in fact all but two of those listed by the commenter do not even examine the issue of the relationship of ETS exposure and asthma severity. The two potentially relevant studies (Bailey *et al.* 1994 and Hong *et al.* 1994), while ostensibly “negative” studies, are far less informative than that of Jindal *et al.* The studies listed in the commenter's attachment A are addressed in the following paragraphs.

Bailey *et al.* (1994) report a primarily descriptive examination of patients served by the Comprehensive Asthma Program of the University of Alabama at Birmingham. Though the investigators apparently examined the prevalence of passive smoking among the 263 of 479 patients served by this clinic program, there were no data on ETS exposure assessment or prevalence or on the relationship of ETS exposure to asthma severity provided in the report, other than that the investigators “found no relationship between asthma severity and ... passive smoking,” and that “exposure at work was more common (for those who worked) than exposure at home.” This report analyzed numerous asthma co-morbidities and potential determinants of severity and asthma management, but, unlike the Jindal study, provides no information about ETS exposure assessment, and hence is difficult to evaluate. The abstract does not even refer to tobacco or ETS.

Flodin *et al.* (1995) is a case-control study of the relationship between smoking (active and passive) and the risk of adult-onset asthma. This study does not address the issue of whether exposure to ETS has an effect on the severity of adult asthma.

Hong *et al.* (1994) examined the influence of numerous lifestyle and behavioral influences on indices of asthma morbidity in 787 of 1352 eligible adult patients, aged 21-54, attending government-run asthma outpatient clinics in Singapore. Asthma morbidity was assessed by questionnaire and the dichotomous outcome variable of “increased morbidity” was designated to include, during the year preceding administration of the questionnaire, ≥ 1 “attack”/week (in the day or at night), ≥ 4 urgent care visits for asthma, ≥ 1 hospital admission, or ≥ 7 days of sick leave. Unlike the Jindal study, which undertook a quantitative assessment of the relationship between ETS exposure and a variety of indices of asthma severity, Hong *et al.* apparently collapsed their indices of severity into a single dichotomous variable, thereby decreasing substantially the likelihood of detecting any effect of ETS exposure. In addition, this study provides no detail about exposure assessment, other than that it was ascertained by questionnaire and that it was treated as a dichotomous variable. Dichotomizing ETS exposure as well would tend to bias the analysis towards the null hypothesis of no effect. These limitations, in addition to potential selection bias (fewer than 65% of eligible patients were included in the analysis) all limit the interpretability and generalizability of this study.

Jedrychowski *et al.* (1995) investigated the effects of passive smoking and gas stoves used for cooking on the prevalence of chronic respiratory symptoms and asthma in women aged 65 or more living in Cracow, Poland. While this study examines potential effects of exposures to indoor air pollution on the prevalence of asthma, it does not address the issue of whether exposure to ETS has an effect on the severity of adult asthma.

Lebowitz (1984) undertook an analysis of the influence of a variety of factors, including air pollution, the use of gas stoves, and exposures to ETS, on the occurrence of respiratory symptoms in asthmatics and nonasthmatics in Arizona. In addition to the major limitations of this study listed below, the report by Lebowitz does not address the issue of whether exposure to ETS has an effect on the severity of adult asthma. Though there were 117 families that participated in this two-year daily time-series study, the number of asthmatics (either children or adults) is not stated in the report. The method of exposure assessment is not articulated either, other than that: the participants completed daily diaries with symptom information and peak flow measurements, and “[a]ll families provided information as to household characteristics.” Indoor air quality monitoring was undertaken on a subsample of 41 homes, including measurements of airborne particles, which were correlated with the presence of smokers in the home (n=19). While this study purportedly examined the acute effects of daily exposures on respiratory symptoms, the analytical approach was not typical of methods in general use for time-series data. The results are not presented clearly. The report states that ETS did not have an effect on peak flow or any daily symptom prevalence in adults, though indoor particles were associated with “several symptoms” in asthmatics and nonasthmatics and with peak flow in asthmatics. However, given the limited information provided in this report, one cannot take such an assertions at face value.

The last two reports listed in the commenters’ Appendix A, Leuenberger *et al.* (1994) and Robbins *et al.* (1993), are discussed on pp. 6-48 - 6-50 of the OEHHA report. These reports both found that chronic ETS exposure is a risk factor for adult-onset asthma. However, these reports do not address the issue of whether ETS exposure affects the severity or control of asthma in adults who already have the disease.

In summary, most of the supplemental references provided by the commenter are not even relevant to the statement in the OEHHA document that they were alleged to address. The two studies that are potentially relevant (Bailey *et al.* 1994 and Hong *et al.* 1994) contribute little information, as described above. However, descriptions of these reports will be added to the final OEHHA report.

4. Comment Summary: The commenter believes that the following statement in the OEHHA document is unsubstantiated. “The results of controlled chamber *investigations* suggest that even single exposures of adult asthmatics to ETS can elicit prolonged airway hyperresponsiveness (AHR), which provides experimental support for the epidemiological observations.” [emphasis added by commenter] Only one citation

(Menon *et al.* 1992) is adduced in support of this assertion, and this study is not adequately discussed elsewhere in the document. In addition, because this is a single report, it is inappropriate to base any conclusions on it. The commenter also cites several quotations out of context from Menon *et al.* (1992) that, in the opinion of OEHHA staff, could mislead the naïve reader. These are reproduced in context below.

Response: The commenter has identified a typographical error, which will be corrected in the final draft to read as follows: “The results of one controlled chamber investigation suggest that even single exposures of adult asthmatics to ETS can elicit prolonged airway hyperresponsiveness (AHR), which could provide experimental support for the epidemiological observations.” The Menon *et al.* (1992) study was one of a series of investigations undertaken at Tulane University examining the effects of ETS exposure on “smoke-sensitive” individuals, including both asthmatics and nonasthmatics. This is the only published report that OEHHA staff were able to identify in which AHR was studied at serial intervals after ETS exposure. We concur with the commenter that it would be inappropriate to “base a conclusion” on a single, unreplicated study; however, that is not what was done here. OEHHA has not “based a conclusion” on this report alone, but rather has cited it as providing some experimental, corroborative evidence for the epidemiological studies. More specifically, the sentence that the commenter found objectionable appeared in the following context:

The above [epidemiological] reports support the existence of an association of chronic or repeated ETS exposure with severity of asthma measured by a variety of indices. In several epidemiological studies, ETS has been implicated as a risk factor for exacerbation of asthma, measured as increases in symptoms, medication use, and clinic or emergency room (Evans *et al.*, 1987; Chilmonczyk *et al.* 1993; Jindal *et al.* 1994; Ostro *et al.* 1994 (see below)). Airway responsiveness, one indicator of asthma severity, tends to be increased in asthmatic children whose mothers smoked in comparison with those with nonsmoking mothers (O'Connor *et al.*, 1987; Murray and Morrison 1989). The results of controlled chamber investigations suggest that even single exposures of adult asthmatics to ETS can elicit prolonged airway hyperresponsiveness (AHR), which provides experimental support for the epidemiological observations (Menon *et al.* 1992). Increased airway responsiveness facilitates bronchoconstriction (and the concomitant symptoms of chest tightness, wheeze, and difficulty breathing) in response to respiratory irritants, such as ETS (NRC 1986). The above findings support the assessment articulated by the U.S. EPA that there is sufficient evidence to support the inference of a causal relationship between ETS exposure and “additional episodes and increased severity of asthma in children who already have the disease.” (pp. 6-6 - 6-7)

The report by Menon *et al.* (1992) is summarized in Table 6-2, and is mentioned in the discussion on pp. 6-9 and 6-10. Briefly, this investigation examined the time course of

AHR in 31 “smoke-sensitive” asthmatics and 39 “smoke-sensitive” individuals without asthma after a 4 - 6 hour controlled exposure to ETS, at high-level, but realistic concentrations. Smoke sensitivity was defined as experiencing lower respiratory symptoms (chest tightness, shortness of breath, cough, or wheeze) or upper respiratory symptoms on exposure to ETS, for the asthmatics and nonasthmatics, respectively. All subjects were atopic – i.e., they were allergic to two or more of 25 allergens. AHR was assessed using a standard methacholine challenge test protocol. Methacholine acts on airway smooth muscle to provoke bronchoconstriction: increased AHR is indicated by decreased quantities of inhaled methacholine needed to elicit a given degree of bronchoconstriction. In this study, the subjects were administered a methacholine challenge test the day before they were exposed to ETS, then two such tests at six and 24 hours after the ETS exposure. If they had increased AHR at 24 hours post-exposure, they were to receive additional methacholine challenges on days 3 and 7 and weekly thereafter until their airway responsiveness returned to baseline. To control for the potential effects of performing serial methacholine challenges, 10 asthmatic subjects repeated the 0, 6, and 24 hour challenges without ETS exposure.

Among the asthmatic subjects, 32% (10/31), 29% (9/31), and 16% (5/31) had increased AHR at 6 hours, 24 hours, and 3 days post-exposure. The last group all showed increased AHR at one week, and 13% (4/31) showed increased AHR at two weeks. Four subjects required rescue bronchodilators with the methacholine challenges at 6 or 24 hours and withdrew from further participation, so these numbers may be underestimates. (All subjects were otherwise asymptomatic, so that the increased AHR was subclinical.) Three subjects showed increases in AHR of eight-to-sixteen fold at 24 hours post-exposure. Smaller percentages of nonasthmatics exhibited increased airway responsiveness post-exposure: 18% (7/39) at 6 hours, and 10% (4/39) at 24 hours. Two subjects, one with and one without asthma, did not return to baseline for eight weeks. . None of the 10 control subjects exhibited significantly increased AHR. Since AHR is generally considered to represent one dimension of airway inflammation, the authors stated that their results suggest that “prolonged subclinical inflammation can occur in the absence of demonstrable change in airway caliber on exposure to ETS.”

Several of the commenter’s quotations are reproduced below in bold, with additional text from the same article in italics.

Whether or not serial MCs (methacholine challenges) within a 24-hour period per se may alter airway susceptibility to subsequent MCs can be questioned. *Prior methacholine administration has not been demonstrated to increase responsiveness to subsequent MCs (citation). On the contrary, a decrease in responsiveness to methacholine has been reported in nonsmoking subjects without asthma serially challenged with methacholine within 24 hours or less (citation). None of the 10 control subjects with asthma in this study who were subjected to three sequential MCs within a 24-hour period, without ETS exposure, demonstrated a twofold or greater decline in PD₂₀ [the minimum criterion for designating*

an increase in AHR] as occurred in some of the subjects after ETS challenge. (Menon et al., 1992, at p. 565)

Clearly, passive cigarette smoke challenge studies performed in the laboratory are limited by experimental conditions and thus cannot always be equated with ETS exposure in real life situation[s].

However, we believe that our finding of increased [methacholine-induced airway hyperresponsiveness] after ETS exposure, even in asymptomatic subjects, is relevant to the issue of cigarette-smoke reactivity. (Menon et al., 1992, at p. 565) While OEHHA staff certainly agree with the substance of the passage quoted by the commenter, the latter has used it to imply that the levels of ETS used in these challenge studies were very unrealistic. In this regard, Menon et al. stated (at p. 564) that “Every effort was made during the challenge to simulate ETS levels similar to levels encountered in real life. The cigarette-smoke levels used in our bronchoprovocation studies have been reported in public places (citation). However, as is the case with allergen challenges, the subjects may have been exposed to relatively higher doses of ETS in a shorter period of time during challenge.”

5. Comment Summary: The commenter takes issue with the statement in the OEHHA report that “There is suggestive recent evidence that ETS exposure may elicit acute symptoms in adults,” and states that all the available population data on reported ETS exposures and symptoms (referenced in its Attachment A) “do not present a conclusive picture.”

Response: This comment is not at variance with the statement in the OEHHA text, which only describes the time-series study by Ostro *et al.* (1994) as “suggestive” not “conclusive”. The studies cited in the commenter’s Attachment A have been summarized in the response to Philip Morris Comment 3. As above, almost all of the studies in Attachment A do not even address the substance of the OEHHA quote. The single report that may be relevant is that by Lebowitz *et al.* (1984), which, as noted earlier, does not specify the number of asthmatic study subjects, provides virtually no information on ETS exposure assessment, uses a statistical methodology uncommon for time-series data, and presents the results unclearly.

6. Comment Summary: The commenter objects to the statement in the OEHHA report that the results of the controlled exposure studies “suggest that there is likely to be a subpopulation of asthmatics who are especially susceptible to ETS exposure.” The commenter suggests that this is inconsistent with a prior statement in the OEHHA report that “[N]either individually nor collectively can these investigations definitively address the issue of whether acute ETS exposure can precipitate an asthma flare.” Moreover, the commenter believes that, although OEHHA discusses a number of limitations of the clinical studies, this discussion is incomplete, and should include additional materials on: (1) the high levels of exposure used in these studies; (2) how asthmatics tend to respond

to a variety of respiratory irritants as well, such as room deodorizers and cooking odors; (3) the likelihood that all the responses observed are due to self-selection of “sensitive” subjects who experience effects due to psychological suggestion; (4) the nonequivalence of statistical and clinical significance, specifically involving statistically significant lung function decrements of less than 20%, which the commenter cites as the clinically significant cutoff, according to anonymous researchers; (5) the withholding of medications prior to testing, which might remove the subjects’ protection against a reaction to ETS exposure; (6) the small numbers of subjects in these studies.

Response: OEHHA staff do not consider the two quotations from the text of the report to be contradictory. Controlled exposure studies typically are limited in their generalizability by a variety of design constraints, most of which tend to underestimate any potential associations between an exposure and respiratory outcomes. These are discussed on p. 6-9, 6-15 and 6-16 of the OEHHA report. However, as noted in section 6.1.1.2, the series of studies at Tulane University indicated that, among subjects selected for subjective “smoke sensitivity”, there was a subgroup with reproducible *physiological* responses to ETS exposure. Their responses did not necessarily constitute asthma “flares” and therefore there is no inconsistency between the two OEHHA statements. Moreover, the commenter appears to agree with the first of the OEHHA statements, albeit with supplemental caveats: “Taken as a whole, the chamber studies suggest that, among self-described “smoke-sensitive” asthmatics, some percentage may exhibit a clinically significant decrement in lung function when exposed to extremely high tobacco smoke concentrations in an artificial situation.” (Philip Morris comments, at p. 7).

Although the results of the controlled chamber studies are already subject to extensive caveats in the OEHHA document in section 6.1.1.2, OEHHA staff have considered the commenter’s suggestions for describing additional limitations of chamber studies, as follows:

- a) Staff concur that, although the exposure concentrations used in the controlled exposure studies are explicitly stated in Table 6-2, a supplemental comment is warranted in the text, indicating that most of the concentrations used tend to be higher than most “normal” exposure situations.
- b) That asthmatics may experience adverse reactions to respiratory irritants other than ETS is irrelevant to this document; hence, no additional comment will be added to address this issue.
- c) The document already indicates that selection bias is a problem with such controlled exposure studies (at p. 6-9) and discusses the issue of psychological suggestion as the explanation for the results seen in some studies (at pp. 6-15 - 6-16); therefore, no additional language will be added to address these issues.
- d) While it is true that some physiological responses can be statistically significant, without being biologically meaningful, in reviewing the results of

the controlled exposure studies noted in Table 6-2, there is little need for such an additional caveat in the OEHHA document, even applying the artificial (20%) yardstick proposed by the commenter. Because of the many limitations on generalizability of the chamber studies, the only inference that OEHHA has drawn from them is noted by the commenter above, i.e., that there is likely to be a subset of asthmatics who are especially susceptible to effects of ETS exposure. Thus, there is little danger of over-interpreting the results of the few studies in which the mean percentage reduction of measures of forced air flow was less than the cutpoint suggested by the commenter. In fact, in a number of these studies, lung function decrements experienced by study subjects exceeded 20%.

- e) OEHHA staff disagree with the commenter with respect to withholding bronchodilator or anti-inflammatory medication prior to ETS challenge. The use of such medications may counteract the acute effects of exposure, and blunt the sensitivity of the experiment (Menon *et al.* 1991). Moreover, many asthmatics in “real life” do not conscientiously adhere to an appropriate medication regimen. Thus, temporary withholding of asthma medications has become generally accepted in protocols for such controlled exposure studies involving a variety of air pollutants, not just ETS.
- f) The issue of small numbers of participants in these studies has already been addressed in the OEHHA document (pp. 6-9 and 6-15).

7. Comment Summary: The commenter disagrees with OEHHA’s statement that “The studies reviewed in this section support the previous findings by the U. S. EPA (1992) that there is ‘sufficient evidence...that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease.’” (p. 6-8 [not p. 6-1, noted in the comment]) The commenter criticizes three studies published after the appearance of the U.S. EPA report (Ogborn *et al.* 1994, Chilmonczyk *et al.* 1993, and Murray and Morrison 1993), and states that OEHHA should also have included a publication focusing on determinants of severe asthma by Strachan and Carey (1995). The commenter believes that “the epidemiological data clearly cannot be cited as supporting a causal association given the magnitude of the relative risks cited, the inconsistencies within the studies themselves, and the fact that no study has adequately controlled for confounding.”

Response: It is important to distinguish between the effects of chronic ETS exposure, which appears to worsen severity and control of childhood asthma, and whether acute exposure to ETS can result in a temporally related exacerbation of respiratory symptoms. The conclusion articulated by the U.S. EPA, and supported by OEHHA, refers to the former. With respect to the latter, the OEHHA document states, “Whether acute ETS exposure can precipitate a specific asthma flare is not so clear-cut...” (p. 6-7) The study by Ogborn *et al.* (1994) focused on the latter issue, but clearly had inadequate statistical

power, as discussed on p. 6-7, so it is not surprising that the commenter would cite this report as showing “no correlation between ETS exposure and exacerbation of asthma.”

In contrast, Chilmonczyk *et al.* (1993 -- discussed on pp. 6-3 - 6-4) examined the relation of chronic ETS exposure and the occurrence of medically documented asthma exacerbations during a one-year period among 199 children attending a large allergy/asthma clinic. Whether assessed by parental questionnaire or by the children’s urinary cotinine levels, ETS exposure was found to be related, in a dose-dependent manner, to the frequency of asthma exacerbations. The commenter criticizes this as a “small study”, which would have greater cogency had this been a null or negative study. Secondly, the commenter asserts that this well conducted study should be reanalyzed because of an apparent typographical error in Table 3, and “because it is impossible to determine the partitioning of the two exposed groups.” OEHHA staff cannot agree with either of these assertions.

The commenter criticizes Murray and Morrison (1993) as “extremely difficult to interpret.” This report (discussed on p. 6-5) indicates that asthma severity and spirometric indices improved among children whose parents smoked less in their presence, though AHR did not show statistically significant improvement. While this last finding was unexpected, it does not, in OEHHA staff’s opinion, render the study “extremely difficult to interpret” or make it otherwise unsuitable for inclusion in the document.

Strachan and Carey (1995) reported the results of case-control study of residential environmental determinants of severe asthma among 763 children, aged 11-16, in Sheffield, England. To be eligible, the child must have had 12 or more episodes of wheezing or at least one speech-limiting attack of wheezing (during which the child could say only one or two words between breaths). Controls who had no history of asthma or wheeze at any age were frequency matched on age and school class. ETS exposure was assessed by parental questionnaire. The analysis focused on factors in the home environment that contributed to status as a case, which was defined as having had at least 12 episodes of wheeze, one or more speech-limiting attacks, or both. The only ETS-related data pertained to three current parental smoking categories: none, 1-10 or >10 cigarettes/day. While paternal smoking was unrelated to the outcomes examined, maternal smoking >10 cigarettes/day was significantly related to the combined category of frequent wheezing plus speech-limiting attacks (crude odds ratio 2.28, $p < 0.05$). However, in models adjusting for numerous other household factors (e.g., current and past pet ownership, type of pillow and bedding used, age of mattress, and so forth), the odds ratio for maternal current smoking was still elevated (1.49) but no longer significant. It is not clear from this report whether the investigators examined the “healthy passive smoker effect,” i.e., whether the parents of children most severely affected stopped smoking because of the children’s asthma. This study examines risk factors for having severe asthma versus not having asthma at all: it does *not* address whether exposure to ETS or other factors influence the severity of asthma among children who already have this disease. Therefore, it does not affect OEHHA’s judgment about the latter issue.

Nevertheless, OEHHA staff will incorporate this summary of the study by Strachan and Carey into section 6.1.1.1 of the report.

In summary, the commenter has not made a compelling case that the data upon which OEHHA has relied are so flawed, inconsistent, or incomplete that they cannot support the conclusion articulated in the report. See also responses to comments 3 and 3a submitted by Raphael Witorsch, comment 1 submitted by the Tobacco Institute, and prior responses to comments submitted by Philip and Raphael Witorsch on behalf of the Tobacco Institute.

8. Comment Summary: The high levels of tobacco smoke used in the three chamber studies involving children did not result in significant effects: therefore, these cast “considerable doubt on the epidemiologic data.”

Response: As noted in section 6.1.1.2 and in responses to Philip Morris comments 4 and 6, the chamber studies suffer from so many design constraints that the generalizability of these investigations is very limited. Some of the specific problems with the three studies cited by the commenter are noted in Table 6-2 and on p. 6-15. In addition, selection bias and low power are considerations in all three. Therefore, OEHHA staff disagree with the commenter’s contention.

9. Comment Summary: The commenter states that the U.S. EPA (1992) did not review eight papers on ETS and lower respiratory illness that had been published prior to 1992, the majority of which had results that were inconsistent with the conclusions stated by OEHHA (p. 6-16), that “It has been clearly established in nearly two dozen reports reviewed by the NRC (1986), the Surgeon General (1986) and the U.S. EPA (1992), that ETS exposure increases the risk of acute lower respiratory disease in young children by 1.5 to 2-fold.” OEHHA did not undertake a *de novo* analysis of this issue, but stated that “More recent published investigations support the conclusions articulated in these reviews.” OEHHA cited three of these (Chen 1994, Robertson *et al.* 1994, and Douglas *et al.* 1994) as examples of studies consistent with this conclusion, but failed to note Forastiere *et al.* 1992, Wolf-Ostermann *et al.* 1995, and Mannino *et al.* 1996, which “do not support claims of such an association.”

Response: The commenter has not made a persuasive case that the conclusions of the earlier reviews are mistaken. The relevant issues are discussed at pp. 6-16 - 6-17 of the OEHHA document. The claim that the three “post-U.S. EPA” reports do not support claims of such an association is inaccurate, as described below.

Forastiere *et al.* (1992) examined the relationships between a variety of predictors and respiratory illness in 2,929 Italian children, aged 7 - 11 years old, in a cross-sectional study in 1987, and found significantly elevated odds ratios in relation to the children’s exposure to passive smoking. For example, the odds ratios (and 95% confidence intervals) for any smoker in the house were 1.3 (95% C.I. = 1.03-1.6) for early respiratory infection and 1.8 (95% C.I. = 1.2-2.7) for night cough. Though the odds ratios were

elevated for either maternal or paternal smoking alone, they were not statistically significant.

Wolf-Ostermann *et al.* (1995) undertook a prospective cohort investigation of respiratory illness in 8,514 German children, with data collection in 1977, 1979 and 1985. They also found a variety of significantly increased odds ratios for several adverse respiratory outcomes; e.g., 1.26 (1.07-1.49) for bronchitis, and 1.55 (1.30-1.85) for fall and winter cough.

Mannino *et al.* (1996) analyzed data from the 1991 National Health Interview survey to estimate the relationships between parental smoking and the occurrence of respiratory illness in children aged 1-10 in the two weeks preceding the interview. They found that ETS-exposed children had 21% more restricted activity days, 31% more days of bed confinement, and 39% more days of school absence than those not exposed (all relationships were highly significant $p < 0.01$). Adjusting for age, sex, family size, socioeconomic status, season, and region, Mannino *et al.* found a higher incidence of acute respiratory illness (RR=1.10, 95% C.I. = 0.95-1.26) and a higher prevalence of chronic respiratory illness (OR=1.28, 95% C.I. = 0.99-1.67). Though these latter estimates were not statistically significant, Mannino *et al.* indicated that, because of the nature of the survey, the study had a power of 0.30 to detect a 10% increase in the two-week incidence of acute illness and 0.60 to detect a 25% increase in the prevalence of chronic disease. The investigators also pointed out a variety of other considerations that would bias their results towards the null hypothesis, such as the dichotomous exposure classification (exposed vs. not exposed).

OEHHA staff disagree with the commenter that these studies, which were not cited in the report (but will be in the final report), fail to support the conclusion stated in the report regarding the relationship between ETS exposure and acute lower respiratory illness in children.

9. Comment Summary: OEHHA defines annoyance only as "a subjective state of displeasure resulting from a defined environmental stimulus." ...OEHHA must provide precise and valid definitions that delineate criteria for including and/or excluding parameters that will define irritation, annoyance, or any of their derivatives or potential synonyms.

Response: Functional definitions of "sensory irritation" and "pathological irritation" have been added to the section. The definition of "annoyance" stands as written.

10. Comment Summary: OEHHA references only three reviews as background information for this claim [that "a substantial body of literature addresses the acute and reversible irritative effects of ETS on the upper respiratory tract."]. Two of three reviews cited are "dated," and none of the literature cited was published since 1992.

Response: As is the case for other sections within this chapter, initial reference is made to previous governmental literature reviews. In this case, the starting points were the Surgeon General's 1986 report, "The Health Consequences of Involuntary Smoking," and

the National Academy of Science's 1986 report, "ETS: Measuring Exposures and Assessing Health Effects." The criticism would be valid if the review stopped there. Given the interval since the original drafting of the report, however, Philip Morris' suggestion that more current references be incorporated is very appropriate, and has been followed (see below).

11. Comment Summary: OEHHA fails to provide direct evidence relating specific constituents in ETS to purported irritation effects. OEHHA simply does not provide any evidence to support its claims that ETS, or constituents of ETS, stimulate the sensory apparatus.

Response: OEHHA staff have reviewed the interval literature, and additionally are grateful to another interested party, R.J. Reynolds, for providing several such references, including some that are pending publication. The following addition will appear in the revised final report:

Text addition: Selected investigators have examined the human sensory and reflex respiratory response to specific ETS constituents. Kendal-Reed *et al.* (1996) demonstrated reflex changes in respiration (decreased tidal volume) among human volunteers exposed briefly (15 sec.) to propionic acid vapor at concentrations of 0.12-85 ppm. Walker *et al.* (1996) examined the olfactory and irritant (trigeminal) properties of nicotine in both humans and experimental animals. The investigators pointed out that, on a part-per-million basis, nicotine was more potent than acetic or propionic acids, or amyl acetate, in eliciting: 1) olfactory sensation (in subjects with a normal sense of smell); and 2) subjective nasal irritation (in subjects lacking the sense of smell). The investigators were able to corroborate their estimates of the relative stimulatory potencies of these compounds by obtaining electrophysiologic recordings from the trigeminal nerve in rats, finding a 15 to 60-fold lower response threshold for nicotine vs. the other study compounds.

12. Comment Summary: This section ["Eye Irritation"] relies upon questionnaire studies of subjectively reported symptoms as evidence of eye irritation. Using OEHHA's definition of annoyance, these studies may arguably fulfill the criterion for annoyance, not irritation.

Response: The eye irritation section refers to both symptom surveys and experimental (chamber) work examining both objective and subjective endpoints. The word "subjective" or "self-reported" has been added to "eye irritation" when the endpoint in question is sensory irritation alone, without objective correlates.

13. Comment Summary: OEHHA proffers three specific articles to support its claim of nasal irritation due to ETS exposure... Two of the studies cited, Bascom *et al.* 1991, and Willes *et al.* (1992) report on a specifically recruited and selected group of "sensitive" individuals. Data from these studies were collected from experimental chambers where subjects were exposed to sidestream tobacco smoke...at a level of exposure that was excessively high [45 ppm CO vs. 2.5 to 13 ppm in natural settings].

Response: Although in a follow-up study the Bascom group did specifically advertise for self-identified "ETS-sensitive" individuals (Willes *et al.*, 1992), the original group of

"historically ETS-sensitive" subjects represented approximately one-third of an unselected sample of questionnaire respondents (Bascom *et al.*, 1991). Further, in an earlier preliminary study, selected subjects showed an increase in nasal airway resistance with STS exposures as low as 15 ppm CO times 2 hours (Bascom and Willes, 1990).

14. Comment Summary: OEHHA states that "despite a lack of evidence for direct allergic mechanisms," referenced data are "implying a modulatory effect of allergy upon the irritant chemoreceptive system." These conclusions are inferred by OEHHA, not by the authors of the studies...

Response: Upon closer reading of the cited reference, Philip Morris reviewers will find the following statement: "The increased responsiveness to ETS among atopic individuals may reflect an antigen-induced neural responsiveness." (Bascom *et al.*, 1991, p. 1310) This point is amplified in a review article by the same author exploring sources of variation in upper respiratory tract irritant sensitivity (Bascom, 1992); this latter reference has been added to the bibliography.

15. Comment Summary: OEHHA does not establish alteration of sensory thresholds as a specific health effect and admits that "reports of altered irritant thresholds due to ETS exposure have not appeared in the literature."

Response: Although variations in irritant perceptual acuity have been reported as a function of active smoking (Dunn, Cometto-Muñiz and Cain, 1982; Shusterman and Balmes, in press), the relationship of ETS exposure and irritant perceptual acuity has not been explored in the published literature. The alteration that has been associated with ETS exposure in at least one study is that of decreased olfactory acuity (Ahlstrom *et al.*, 1987). In addition to contributing to overall quality-of-life, olfaction serves as a warning factor for ingestion of spoiled food, for escape from fires, and for exposure to noxious airborne agents in the workplace. OEHHA therefore defends the inclusion of this sensory alteration under the rubric of "health effects."

16. Comment Summary: OEHHA simply does not provide any evidence that odor annoyance is a health effect.

Response: In California, air emissions that are "offensive to the senses" have typically been dealt with under the Health and Safety Code (see Section 41700), setting a precedent for them to be considered "health effects."

17. Comment Summary: OEHHA attributes a claim to Cain *et al.* (1983) that "when smokers and nonsmokers occupy the same air space, air dilution rates required to render odorant levels acceptable to nonsmokers may be unrealistically high from an engineering standpoint," when in fact this reference is actually attributable to Samet *et al.* (1991).

Response: In the secondary citation referred by Philip Morris (Samet, Cain and Leaderer, 1991), the authors review previous primary studies, including Cain *et al.* (1983). That chamber study looked at ETS-related odor intensity and air quality acceptability as a function of occupant smoking rate, air exchange rate, temperature, and humidity. The authors stated: "None of the conditions in the present investigation would satisfy even 2/3 of non-smokers." (P. 1191) They further noted: "It seems likely that previously adsorbed tobacco smoke causes the bodies and clothing of smokers to emit more odorous

material than those of nonsmokers..." (p. 1190), indicating an emission problem from smokers even in the absence of active smoking. In the secondary reference (Samet, Cain and Leaderer, 1991), the authors point out that "visitor" studies such as Cain *et al.* (1983) may actually overestimate the degree of acceptability of ETS-polluted indoor air because upper respiratory tract irritation is time-dependent, whereas the "visitor" role involves only intermittent sampling ("sniffing") of the atmosphere in question, placing emphasis upon perceived odor as the criterion for acceptability.

18. Comment Summary: The commenter states that there are "clearly a significant number of errors in the OEHHA meta-analysis relating ETS exposure to asthma induction in children." Where there were multiple estimates of relative risk in several studies, the commenter objects to OEHHA's choice of estimates, as follows: (1) In the Andrae *et al.* (1988) study, the commenter would have used 0.9 rather than 2.5, since the latter estimate was limited to homes where dampness was present, while 0.9 reflected the estimate where home dampness was absent. (2) In the Burchfiel *et al.* (1986) study, the RR estimate used was 2.16, which applied to boys only when both parents smoked, rather than the estimate of 1.05, which applied to girls. (3) Chen (1988) reports no increased risk for asthma induction associated with ETS exposure. (4) Duff *et al.* (1993) should have been included only in the analysis of wheezing and not "clinically recognized asthma." (5) In the Martinez (1992) study, the RR is 1.03 for maternal smoking for mothers with >12 years of education, yet OEHHA used the crude RR of 1.68. (6) OEHHA uses the higher estimates of RR associated with maternal smoking, when the meta-analysis is not stated to be restricted to maternal smoking. (7) OEHHA's discussion of heterogeneity among results is inadequate, especially the paragraph that indicates that the RRs based on cotinine-assessed exposure were higher than those based on questionnaire data, since these studies were not referenced.

Response: There is only one bona fide error of the seven listed by the commenter: the Duff *et al.* study should have been included in the analysis of "wheezy bronchitis" rather than clinically diagnosed asthma. Making this change results in the following estimates: for asthma, RR = 1.44 (95% C.I. = 1.27-1.64) and for wheeze RR = 1.47 (95% C.I. = 1.34-1.61). These should be compared with the estimates in the OEHHA document of 1.45 (95% C.I. = 1.28-1.65) for asthma, while the estimate for wheeze did not change. OEHHA staff also undertook an influence analysis, in which one study was dropped at a time and the pooled RRs were re-estimated. No single study (including all of those listed by the commenter) had a significant effect on the pooled estimates.

Contrary to what the commenter indicates, the Chen (1988) study does provide information from which an estimate of relative risk for asthma can be calculated (See Table 5 of that article). For the Andrae *et al.* (1988) study, one cannot use the RR estimate of 0.9 suggested by the commenter, since it was unaccompanied by a confidence interval or standard error, at least one of which is required to perform the pooled estimations. In the Martinez *et al.* (1992) article, OEHHA used an estimate of relative risk of 1.59 (95% C.I. = 1.03-2.44), which represented the risk of developing asthma among mothers who smoked 10 or more cigarettes/day, adjusting for the child's gender and reported parental respiratory symptoms. When stratified on maternal educational

level (an indicator of socioeconomic status), Martinez *et al.* reported RRs, adjusted for the child's gender, of 1.03 (95% C.I. = 0.61-1.75) when the mother had greater than a high school education, and 2.55 (95% C.I. = 1.42-4.59) when she had 12 years of schooling or less. The commenter mistakenly suggests that OEHHA used the estimate of 1.68 (95% C.I. = 1.10-2.58), which represented the estimate for maternal smoking of at least 10 cigarettes/day, adjusted for the child's gender.

In order to examine how the pooled estimates would change if the commenter's suggestions were adopted (regardless of the merit of these suggestions), OEHHA repeated the analysis, correcting the placement of the Duff *et al.* study, deleting the estimate from the Andrae study, and using the low estimates of 1.03 (instead of 1.59) from the Martinez study and 1.05 from the Burchfiel study (instead of 2.16). These changes, not surprisingly, reduced the magnitude of the pooled RR estimate for clinically diagnosed asthma from 1.45 (95% C.I. = 1.28-1.65) to 1.33 (95% C.I. = 1.20-1.48). (The wheeze estimate was not affected by these changes, since with the exception of Duff *et al.*, these changes were pertinent only to the clinical asthma category.) Also, though the meta-analysis was not restricted to studies examining only maternal exposure, OEHHA compared the pooled estimates for asthma RRs for studies in which there were separate estimates for maternal smoking versus those for general household smoking. When exposure was related to maternal smoking the pooled RR was 1.60 (95% C.I. = 1.29-1.99), while that for household smoking generally was 1.34 (95% C.I. = 1.11-1.61).

Finally, when exposure was assessed using urinary or salivary cotinine measurements, the pooled estimate was 2.52 (95% C.I. = 1.61-3.95). Because this estimate was based on only four studies (Clark *et al.* 1993, Duff *et al.* 1993, Ehrlich *et al.* 1992 and Willers *et al.* 1991), it combined the outcome categories of wheeze and clinical asthma.

19. Comment Summary: The commenter disagrees that the Bradford Hill "criteria" for causal inference are satisfied with respect to the characterization of ETS as a risk factor for induction of asthma, particularly in young children. The commenter is mainly concerned that:

- a) "statistical significance" has mistakenly been used to satisfy the criterion of "strength of association";
- b) despite the heterogeneity of results noted earlier, OEHHA characterized the ensemble of effect estimates as being "of similar magnitude" in order to meet the criterion of "consistency"; and
- c) there was no discussion of confounding, which is also one of the Bradford Hill criteria.

Response: The oft-cited Bradford Hill criteria are informal guidelines for considering causal inferences, not rigid standards. The discussion in the OEHHA document was meant to be illustrative of this process. Nevertheless, the commenter makes the useful point that this discussion could benefit from clarification. The following modification and

additional text will be added to pp. 6-34 and 6-36, in the sections indicated by the commenter:

- a) “As can be seen in Figures 6.1 and 6.2, most of the estimates of relative risk extracted from the investigations were statistically significant. Of the 37 studies included in the meta-analysis, 14 had point estimates greater than 2.0, suggesting a strong association between ETS exposure and the occurrence of childhood asthma. (strength of association);
- b) “Recognizing the heterogeneity indicated during the process of creating pooled estimates in the meta-analysis, almost all studies had point estimates of relative risk significantly greater than one, and most were statistically significant, whether the outcome was clinically diagnosed asthma or wheezy bronchitis. If there were no relationship between ETS and childhood asthma, one would expect a random distribution of point estimates above and below the null value. This consistency is apparent despite the diversity of study designs and populations. (“consistency”)”
- c) Consideration of confounding is an essential aspect of causal inference, but it is not typically considered one of the Bradford Hill criteria, notwithstanding the commenter’s statement to the contrary. Nevertheless, the following passage will be added to page 6-36: “In epidemiological studies, a confounder is a factor or variable that is associated with both the disease outcome and with the exposure of interest, and can produce a distortion of the relationship (or lack thereof) between the exposure and the disease outcome. The effect of a potential confounding variable can be addressed in the design phase of a study, or if data on the putative confounder are collected during the study, then the potentially distorting effects of the confounder can be controlled for statistically during the analysis. In any given study, there are likely to be few potentially confounding exposures sufficiently important to control for. For studies examining the relationship between childhood asthma and ETS exposure, probably the most important variables to be evaluated as potential confounders, given the current state of knowledge, include the child’s age, history of atopy or allergy, parental history of asthma, allergy or other respiratory symptoms, and an indicator of family socioeconomic status, while other variables that ideally should be examined and adjusted for, if necessary, would include the child’s gender, whether the child was breast-fed in infancy, type of fuel used for heating and cooking, the presence of allergens recognized to be risk factors for induction of asthma (e.g., from household pets or dust mites), home dampness and/or mold, serious lower respiratory infection in early childhood, number of siblings, and maternal smoking during pregnancy (to the extent that this can be segregated from post-natal exposure). Approximately 2/3 of the studies included in the meta-analysis controlled for three or more potential confounders and effect modifiers, and these studies tended to have greater estimates of relative risk of asthma than those studies that adjusted for fewer than three covariates. The association of ETS exposure with asthma was usually found to be independent of these various risk factors.

Several studies examined or adjusted for ten or more potential confounders, and some adjusted for many more, e.g., Infante-Rivarde (1993) apparently adjusted for nearly two dozen variables, reporting an odds ratio of 2.77 (95% C.I. = 1.35-5.66) for maternal smoking of at least one pack of cigarettes/day. Nevertheless, routine adjustment for a long list of putative confounders is methodologically undesirable as it may affect the precision and therefore the significance of the estimate of the relationship between ETS exposure and disease.”

20. Comment Summary: The commenter does not agree with OEHHA’s reliance on the conclusions reached in the three major federal reviews of the evidence that, “a causal relationship is the most likely explanation of the consistently observed associations between ETS exposure and respiratory symptoms in children.” (p. 6-38). As noted in OEHHA’s previous response to similar comments (pp. A-23 - A-24), rather than re-invent the wheel, the conclusions of the three previous national evaluations of this subject were reviewed by OEHHA staff, and their findings were incorporated in summary form, along with the results of a few more recent studies. The commenter observes that in two of the examples cited in the OEHHA report (Goren *et al.* 1995, Henderson *et al.* 1995), the associations between ETS exposure and several outcomes, though significant, were relatively weak.

Response: The results of dozens of studies, involving tens of thousands of children, served as the basis for the conclusions reached by the National Research Council (1986), the Surgeon General (1986), and the U.S. EPA (1992). The conclusions cited by the U.S. EPA is cited in part by OEHHA at p. 6-38:

“There is sufficient evidence for the conclusion that ETS exposure at home is causally associated with respiratory symptoms such as cough, phlegm, or wheezing in children. The evidence is particularly strong for infants and preschool children; in this age range, most studies have found a significant association between exposure to ETS...and respiratory symptoms in the children, with odds ratios generally ranging between 1.2 and 2.4...The evidence is significant but less compelling for a relationship between exposure to ETS and respiratory symptoms in school-age children. Odds ratios for this age group are usually between 1.1 and 2.0...[T]here are significant differences in susceptibility to ETS between individuals. [S]everal factors may amplify the effects of passive smoking: prematurity, a family history of allergy, a personal history of respiratory illness in early childhood, and being exposure to other environmental pollutants.”

The relative risks cited by the commenter for the study by Goren *et al.* (1995) (i.e. from 1.20 to 1.41) are well within the range for school-age children noted in the above passage. This was a cross-sectional study of respiratory health of 8,259 second and fifth grade children in Israel. The commenter did not add that the difference in outcomes listed in

this comment between children exposed and not exposed to passive smoke were all highly significant, with the exception of the association of “wheeze without cold” in association with paternal smoking (for which $p=.02$). In the logistic models used in the analysis, however, the investigators examined (at least) parental respiratory illness, other home exposures, community air pollution, and a crowding index. In addition, Goren *et al.* found significant exposure-response trends for the outcomes of “cough with cold,” “cough and sputum,” “wheezing with cold,” “lung diseases,” asthma, pneumonia, and ear infections.

The commenter suggests that measurement error may explain some of the association of ETS with respiratory illness, citing Henderson *et al.* (1995), which examined a variety of correlates of wheezing in 343 children aged 7 - 11 in North Carolina. As noted in the OEHHA document, Henderson *et al.* reported odds ratios of 2.9 (95% C.I. =1.2-7.0) for ETS exposure in relation to risk of wheeze in nonallergic children and 4.4 (95% C.I. =1.2-16.1) in allergic girls but not allergic boys. The commenter claims that Henderson calculated a relative risk of 2.8 for boys that was reduced to a nonsignificant 1.21 when recalculated using cotinine concentrations. OEHHA staff were unable to find this information in the published report, and the commenter did not provide the calculations, so OEHHA staff cannot respond to this aspect of the comment. Henderson *et al.* appear to be unaware of the alleged impact of measurement error on their study: they estimated that the ETS-attributable risk for wheeze in children, based on their data, was between 15 and 20%.

See also the response to Comment 5 submitted by the Tobacco Institute.

21. Comment Summary: The commenter criticizes two studies cited in the U.S. EPA report as a basis for speculating that ETS-related reductions in lung function may persist into adulthood. By implication, presumably, this is a criticism of the OEHHA document, which states “[R]eductions in lung function in childhood may persist into adulthood and increase the risk of developing chronic obstructive pulmonary disease. The likelihood of such potential long-term consequences has not been fully evaluated.” (p. 6-39 - 6-40, citing the Surgeon General (1986), the NRC (1986) and the U.S. EPA (1992)).

Response: These observations in the OEHHA report about the persistence of lung function deficits does not rest solely on the two references cited in the U.S. EPA report.

22. Comment Summary: The commenter disagrees that the reports on ETS and lung function described in the OEHHA document tend to support the conclusions reached earlier by the NRC, the Surgeon General, and the U.S. EPA. The commenter lists a few criticisms about several of the studies listed by OEHHA. Most require no response. However, the commenter notes that the two studies by Cunningham *et al.* (1994, 1995) were “included as supporting evidence for the purported association of ETS exposure and decreased lung function in children, but neither study actually supports this claim.”

The commenter also takes issue with the statement in the OEHHA description of the report by Cook et al (1993) that, “every lung function index (FVC, FEV₁, FEF₂₅, FEF₅₀, FEF₇₅, and FEV₁/FVC) was negatively associated with salivary cotinine, and all but the FEV₁/FVC ratio were highly significant statistically.” The commenter observes that the FEV₁/FVC ratio was not negatively correlated with salivary cotinine.

Response: OEHHA included the Cunningham reports because they were relevant to the relationship of ETS and lung development, and suggested the potential importance of prenatal or early post-natal exposures. The two studies referred to by the commenter were introduced in the OEHHA report as follows: “Two recent reports by Cunningham and colleagues (1994 and 1995) suggest that prenatal or very early post-natal exposures to tobacco smoke components may affect lung development, inducing persistent effects that may be detected throughout childhood.” Each study found that current maternal ETS was not associated with lung function deficits in children in the age range 8-12 after adjustment for smoking during pregnancy. However, as noted by Cunningham, “The larger associations between maternal smoking during pregnancy and measures of flow rather than volume are consistent with an effect of exposure *in utero*, but early post-natal exposure cannot be ruled out as an alternative explanation for the results of this study.” The same Harvard group also reported that lung function deficits in children (between the ages of 6 and 18) appear to be related to both persistent effects of early childhood exposure *and* additional decrements due to current exposure (Wang *et al.* 1994).

Similar issues were raised in Comment 3f submitted by Raphael Witorsch and Comment 6 submitted by the Tobacco Institute. Please see responses to those comments.

As for the commenter’s observation regarding the relationship of salivary cotinine and the FEV₁/FVC ratio in the study by Cook *et al.* (1993), OEHHA staff concur. Though the coefficient relating these variables was negative, it was not statistically significant, unlike those for the other five lung function measures, which were all highly significant. Therefore, OEHHA will revise the text to reflect this, as follows: “several indices of lung function (FVC, FEV₁, FEF₂₅, FEF₅₀, FEF₇₅) were negatively associated with salivary cotinine; all coefficients were highly significant statistically. Only the ratio FEV₁/FVC was not correlated with salivary cotinine.”

Michael Glovsky for Philip Morris

1. Comment Summary: The commenter reviews some of the recognized causes of asthma, including genetic predisposition, exposure to allergens and certain viral infections. He then states that it is not possible to study the relationship of ETS to causation of asthma except where “individuals are non-atopic (i.e., not allergic), with no family history of asthma; and who had no viral illness. Also the presence of known allergens such as cats, dogs, cockroaches, mites and molds would have to be excluded.”

Response: The commenter is apparently not familiar with well established principles of epidemiology or with the concepts of multivariate regression analysis. The variables that

he mentions are risk factors for asthma that can be controlled for in either the design and analysis phases of a given epidemiological study.

2. Comment Summary: The commenter lists several additional reasons why he believes that epidemiological data on ETS are flawed, including:

- a) the use of questionnaire data to determine exposure to ETS
- b) the relative dearth of studies that have used nicotine-related markers for ETS exposure (i.e., urinary cotinine or nicotine air levels);
- c) the failure to control for many variables such as socioeconomic [status], crowded households, lack of medical care, number of pets, and relative pollution in the external and internal air [which] would confound any statistics”;
- d) there is no animal model showing that ETS can cause prolonged bronchial asthma
- e) no studies show ETS can cause asthma in nonasthmatics

Response: Questionnaire data on exposure to ETS can result in misclassification of exposure. If the focus of investigation is childhood asthma, the most relevant questions concern maternal smoking in early childhood. If there is nondifferential misclassification of exposure, that is, if mothers misreport their smoking regardless of the child’s asthma status, then the overall impact of this misclassification is to decrease the magnitude of any reported association between ETS exposure and induction of asthma. Such nondifferential misclassification would be most likely to occur in prospective studies before any child had yet developed asthma (e.g., Martinez *et al.* 1992). In cross-sectional or case-control studies, such nondifferential misclassification may also occur, but in addition, there could be differential misclassification -- usually involving misrepresentation by smoking mothers who claim to be nonsmokers. This kind of differential misclassification is also likely to result in a downward bias in the estimate of any effect of ETS. While it would be desirable to have more studies in which there are serial cotinine measurements documenting the extent of ETS exposure, this does not mean that all studies that have not measured this biomarker are invalid.

In epidemiological studies, a confounder is a factor or variable that is associated with both the disease outcome and with the exposure of interest (in this case, exposure to ETS), and can produce a distortion of the true association between the exposure and the disease outcome. If data on such confounders are collected during the course of a given study, then the potentially distorting effects of the confounder can be “controlled for” statistically during the analysis. However, some of the “confounders” listed by the commenter are not likely to be confounders at all, such as “relative pollution in the external ... air.” For variables such as this to be considered confounders, one would have to posit that they are distributed differently among children whose parents are smokers and those who are not. Others, such as “socio-economic status (SES)”, “crowded households” and “lack of medical care” are likely to be highly inter-correlated. In many of these studies the investigators have controlled for at least one aspect of SES, as well as having an index for crowding, data on exposure to pets, information on indoor sources of pollution. In the meta-analysis of asthma induction in relation to ETS exposure in

Chapter 6, those studies that controlled for three or more covariates tended to produce higher estimates of effect than those that did not. Some studies adjusted for up to 22 covariates (Infante-Rivarde *et al.* 1993).

That there is no good animal model showing that ETS can cause prolonged bronchial asthma does not invalidate studies in humans. There is no good animal model for human asthma, period. There are a variety of human illnesses that do not occur naturally in animals: this does not mean that these illnesses cannot be investigated until an animal model is developed.

The basis for the commenter's last assertion that there are no studies showing that ETS can cause asthma in nonasthmatics is not clear. The weight of the evidence in the reviews by the U.S. EPA and, more recently, by OEHHA staff indicates that ETS exposure is a risk factor for induction of childhood asthma.

3. Comment Summary: The commenter disputes that ETS exposure may account for numerous exacerbations of asthma in children in California. Then he notes that asthmatic airways are susceptible to a wide variety of exogenous influences, including cold air, air pollutants, irritant chemicals ("including ammonia, Clorox, detergents, metal dust, as well as ETS and other irritants"), infections, and other factors. He then states that, in his clinical experience, he has had only one patient develop asthma in response to massive smoke exposure, and that anecdotally, "there are very few cases of asthma that come to our center ... where a definitive exposure to ETS is known as the major exacerbating agent."

Response: On the one hand, this comment disagrees with the OEHHA document that ETS may exacerbate asthma, while on the other, acknowledges that respiratory irritants, including ETS, can affect the severity of asthma. While the commenter may have extensive clinical experience with asthmatics, his recounting of a single anecdotal case of asthma induction after massive irritant exposure is not equivalent to a systematic, published investigation of ETS-related effects, nor is it even relevant to the issue of asthma exacerbation in people who already have the disease. The commenter also acknowledges some cases of asthma exacerbations who have presented to the health-care facilities where he has worked appear to be related to ETS exposure. However, here also, he presents no data to respond to. Moreover, most exacerbations of asthma, regardless of etiology, would not be expected to result in a visit to a health-care provider or an admission to hospital.

4. Comment Summary: The commenter puts considerable weight on several controlled exposure studies conducted at Tulane University (cited in the OEHHA draft report), which typically involved exposure to relatively high levels of ETS, and finds that extrapolating the results of these studies to childhood exposures is "somewhat inconceivable". He also indicates, in general terms, that the epidemiological studies are flawed, and that "Only prospective controlled blinded studies could provide valid data that would be useful for assessing health effects of environmental tobacco smoke."

Response: The results of the controlled exposure studies were not quantitatively extrapolated to pediatric exposures in the OEHHHA document. As noted in the report (pp. 6-8 to 6-9), such investigations are subject to numerous limitations and biases that restrict their generalizability. In addition, the OEHHHA report noted that the evidence that ETS exposure can precipitate a specific flare or exacerbation of asthma is not clear-cut (p. 6-7). However, epidemiological investigations of children have concluded that regular ETS exposure is associated with an increased frequency of asthma exacerbations (e.g., Evans *et al.* 1987; Chilmonczyk *et al.* 1993). Others (e.g., O'Connor *et al.* 1987) have indicated that regular ETS exposure is associated with increased airway hyperresponsiveness (AHR), which facilitates bronchoconstriction and related symptoms in response to exposure to respiratory irritants). Section 6.1.1.1 summarizes the epidemiological evidence supporting the conclusion reached by both the U.S. EPA and OEHHHA that there is a causal relationship between ETS exposure and “additional episodes and increased severity of asthma in children who already have the disease.” Unlike the commenter, OEHHHA staff believe that one can derive useful information about health effects of exposure to ETS from epidemiological investigations. The specific study designs of “prospective controlled blinded studies” suggested by the commenter, as an alternative to epidemiological investigations, are likely to be subject to the same kinds of selection bias and other limitations as the chamber studies cited in the OEHHHA report, and are therefore unlikely to provide the “valid data” suggested by the commenter.

5. Comment Summary: The commenter asserts that the estimates of ETS-attributable cases of bronchitis in the OEHHHA report are difficult to assess because they are based on modifications of work presented in reports on ETS authored by the National Research Council and the U.S. EPA, which he apparently has been unable to obtain.

Response: The two national reports, which are frequently referenced in the OEHHHA document and are found in the references for Chapter 6 (as well as other chapters), are public documents that are readily accessible and have been widely circulated. If the commenter does not wish to purchase the documents, they are both catalogued in the libraries of the University of California at Los Angeles and the University of Southern California, both of which are accessible from his office at Huntington Hospital.

The Tobacco Institute

Raphael Witorsch for The Tobacco Institute

1. Comment Summary: OEHHHA mistakes statistical significance for causal inference. The commenter apparently believes that epidemiological studies that demonstrate increased risks for certain outcomes are likely to due more to bias and confounding than a real ETS effect, so long as the increase in relative risk (or odds ratio) is less than two or three. More specifically, “causal inferences cannot be made from risk ratios that are in the range described for the respiratory effects of ETS in children, i.e., means of less than two.” This is as true of pooled estimates from meta-analysis as it is of single studies.

Response: If this categorical statement were true, then much of what passes for clinical knowledge in medicine today is without epistemological foundation. Weak associations (i.e., with relative risks or odds ratios < 2) are found in many areas of medicine and, in conjunction with other aspects of causal inference, constitute the basis for a variety of clinical and public health interventions to prevent or ameliorate disease. OEHHA staff are aware of the subtleties of causal inference in epidemiology (for example, see Rothman KJ, ed. Causal Inference, Chestnut Hill, MA, Epidemiology Resources Inc., 1988), and most assuredly have not posited causal relationships on the basis of any single study, which is what the commenter seems to imply. The meta-analyses in the document are not meant to provide only summary estimates of effect, but to afford an opportunity to explore some of the factors underlying the differences in study results. For example, two important findings of this analysis were that case-control studies that used population-based controls and the set of studies that examined ETS exposure in preschool children produced higher pooled estimates of risk of asthma, with little evidence of heterogeneity, than other study subgroups (see pp. 6-33 - 6-34).

2. Comment Summary: OEHHA has used an approach to risk assessment that is deterministic rather than probabilistic, resulting in point estimates rather than ranges of risk for specific outcomes. It would be more appropriate to present quantification of the components of uncertainty underlying these risk assessments.

Response: The risks for some of the outcomes related to ETS exposure are presented as ranges (e.g., asthma induction and exacerbations), while others are presented as point estimates (e.g., lung cancer) (page ES-3). To the extent that the risk assessments are based on epidemiological studies, the quantification of the magnitude of the uncertainties underlying the risk estimates is problematic, since, in general, the studies themselves do not provide sufficient information to judge the extent of exposure misclassification (which would generally, but not always, bias the risk estimates downwards), selection bias, and so forth, so that this information (or lack thereof) cannot be incorporated into the risk assessments.

3. Comment Summary: “The literature demonstrates that a balanced evaluation has not taken place.” Also, “our continuing review of the literature has also discovered papers that were cited neither in the OEHHA document or our initial comments.” The commenter then provides lengthy discussions of his evaluation of the literature related to asthma exacerbation, respiratory infections, otitis media, asthma induction, chronic respiratory symptoms, lung development, and cystic fibrosis.

Response: OEHHA staff believe that the evaluation of the literature is balanced and objective. In fact, the bulk of the commenter’s summaries of recent literature is not substantially at variance with that found in the OEHHA document, as described below, though his conclusions are different. With respect to the papers that were not cited in the OEHHA document, most of the relevant published papers listed in the commenter’s submission are included in the OEHHA document. Most of the other potentially relevant

papers are discussed in these responses to comments. However, the commenter has also listed a number of textbooks and abstracts, which are not addressed either in the document, or in the responses that follow.

3a. Comment and Response -- Asthma exacerbations: The commenter focuses on minor inconsistencies in the lung function data in the Chilmonczyk *et al.* (1993) study and on a number of controlled chamber studies with respect to the question of the relationship of asthma exacerbations to ETS exposure. He does not criticize the main finding of the Chilmonczyk study, which was that, whether assessed by urinary cotinine or by parental reporting, ETS exposure in children was found to be associated with frequency of asthma exacerbations in a dose-dependent manner. As for the results of the various controlled exposure studies cited in his comment, he states, “[T]he additional studies do not consistently support the contention that machine generated ETS acutely evokes adverse physiological changes in the pulmonary system of most asthmatics. The consistent observations of the Stankus group ... suggest a small subset of asthmatics may respond to acute exposure with decrements of respiratory flow rate of 20% or greater, as well as increased responsiveness to bronchoconstrictors...As noted in our initial comments [on the prior OEHHA draft report], the inconsistencies of pulmonary responses of adult asthmatics to ETS exposure could have several explanations, among these is the existence of small subset of hypersensitive asthmatics and/or flaws in the experimental design of selected studies.”

The commenter’s summary is not very different from conclusions in the OEHHA document, which states: “The controlled exposure studies do not clearly demonstrate a consistent effect of acute ETS exposure on asthmatics as a whole...General design constraints in such studies militate against finding effects, *e.g.*, small sample size, systematic exclusion of potential participants who have recently been ill or those with brittle asthma, acute exposures only. Each of these studies has one or more weaknesses in design or analysis; thus, neither individually nor collectively can these investigations definitively address the issue of whether acute ETS exposure can precipitate an asthma flare...[A]lthough the design constraints of the chamber studies limit the interpretation of the results, they do suggest that there is likely to be a subpopulation of asthmatics who are especially susceptible to ETS exposure.” (pp. 6-15 - 6-16)

3b. Comment and Response – Respiratory Infections: The commenter reiterates comments submitted previously regarding problems with epidemiological studies investigating the relationship between parental smoking and early childhood respiratory illness. OEHHA staff have responded to these comments previously (pp. A-22 - A-23). The commenter also cites several studies that found that maternal smoking during pregnancy appeared to exert a stronger effect on lower respiratory illness in early childhood and lung function in infants and older children (aged 8 - 12), than did post-natal exposure. On the basis of these few studies, the commenter suggests that pre-natal exposure represents the mechanism underlying the consistent findings of ETS-associated lower respiratory illness in early childhood.

This comment combines studies of lower respiratory illness with those examining lung function. Studies cited by the commenter focusing on pre-natal exposure on childhood lung function are already included in the OEHHA document (i.e., Cunningham *et al.* 1994; Hanrahan *et al.* 1992), and are described as suggesting “that *in utero* or early childhood exposures to ETS may result in changes in lung development that may persist through childhood and adolescence.” (p. 6-34) Though the commenter interprets these data as indicating a lack of effect of postpartum exposure, Cunningham *et al.* could not distinguish pre-natal from early childhood ETS exposure in their data.

With respect to respiratory infections, while decreased lung function found in infants exposed to maternal smoke *in utero* may predispose them to wheezing lower respiratory infections, the OEHHA document summarizes evidence for an increased risk of nonwheezing illness as well. Moreover, as noted in the OEHHA document, exposure to maternal smoking *in utero* is not a necessary pre-condition for an increased ETS-related risk of respiratory illness in early childhood, as is evidenced by the series of studies by Chen (1986, 1988, 1989), in which the children had nonsmoking mothers but were exposed to household smoke from other sources.

3c. Comment and Response – Otitis Media: After taking into consideration the OEHHA papers and our analysis, we concluded that of a composite list of 24 papers, only 10 report a statistically significant association between outcome and parental smoking...

The point raised by Dr. Raphael Witorsch is identical to that raised by Dr. Philip Witorsch with reference to the May 1994 draft report "Respiratory Health Effects of Exposure to Environmental Tobacco Smoke." OEHHA Staff previously responded to these comments, and the response is belatedly included in the appendices to this report (see above).

3d. Comment and Response – Asthma induction: The commenter reiterates comments submitted and responded to previously regarding the evidence for induction of asthma. In prior comments, reference was made to a table in a paper co-authored by the commenter, in which it was asserted that only 5 of 21 papers examining this relationship showed a statistically significant association. In these comments, the authors list an additional 21 papers purporting to examine this relationship, of which 7 are noted to demonstrate statistical significance. Apart from the accuracy of the commenter’s characterization of these studies, such a “vote count” can be misleading because it ignores the roles of statistical power, bias, and other aspects of study design in determining the results of multiple studies. This is why such a traditional “qualitative tally should never serve as anything more than a provocative introduction to a more detailed analysis (Greenland 1987).” Such an evaluation is provided in the meta-analysis in the OEHHA document (pp. 6-32 - 6-37), the results of which support the existence of a consistent relationship between maternal smoking and the occurrence of asthma in early childhood. The commenter apparently concurs with this assessment when he states, “In young children, asthma incidence is consistently associated with parental smoking in agreement with findings for other clinical endpoints.”

3e. Comment and Response – Chronic respiratory symptoms: The commenter reiterates his position submitted previously, challenging the “OEHHA position that epidemiological studies have linked chronic domestic ETS exposure with recurrent symptoms of cough, wheeze, and excess phlegm in children.” The commenter has also updated his “vote count” of studies submitted previously in support of his position. As noted in OEHHA’s previous response to these comments (pp. A-23 - A-24), rather than re-invent the wheel, the conclusions of the three previous national evaluations of this subject were reviewed by OEHHA staff, and their findings were incorporated in summary form, along with the results of a few more recent studies. The results of dozens of studies, involving tens of thousands of children, served as the basis for the conclusions reached by the National Research Council (1986), the Surgeon General (1986), and the U.S. EPA (1992). The commenter provides another “qualitative tally”, with its attendant limited information, and presents selected results from a few studies reporting significant associations with some symptom endpoints in some subpopulations, but not others. For example, he states, “Eight new studies pertain to cough as an endpoint. Of these 6 report a significant association while 2 do not.” The limited information on this topic submitted by the commenter does not, in OEHHA’s staff’s opinion, constitute a persuasive basis for rejecting the findings of the prior national reviews and studies published subsequently. See also the response to Comment 5 submitted by the Tobacco Institute, below.

3f. Comment and Response – Lung development: The commenter reiterates his position submitted previously, to the effect that studies of childhood ETS exposure are inconsistent with respect to a potential effect on lung growth and development. The commenter has also updated his “vote count” of studies in support of his position, with 17 “new studies” which he asserts that OEHHA has not considered, with the exception of Lebowitz *et al.* (1992) and Sherrill *et al.* (1992). However, on pp. 6-41 - 6-44 and 6-56 - 6-57, the OEHHA report also discusses Wang *et al.* (1994), Rona and Chinn (1993), Haby *et al.* (1994), Cook *et al.* (1993), Cunningham *et al.* (1994 and 1995, one of which was not cited by the commenter), Smyth *et al.* (1994) and Kovesi *et al.* (1993), the last two of which were studies of patients with cystic fibrosis. As noted in our prior responses to comments (p. A-24), this set of outcomes was extensively reviewed at the federal level and, in order to avoid a duplication of effort, OEHHA staff did not undertake a *de novo* reassessment of dozens of studies, but rather summarized the evidence from the three federal reviews, and added information from the more recent papers noted above. In the view of OEHHA staff, recent evidence generally tends to support the conclusions reached by the national reviews, but suggests that effects on lung growth and development may be attributable in part to persistent influences of maternal smoking during pregnancy. The commenter notes, as does the OEHHA report (pp. 6-43 - 6-44), data on the relationship of ETS exposure to childhood lung function are not fully consistent. The OEHHA report indicates that the reasons for these inconsistencies “may be explicable by the crudeness of questionnaire-based exposure assessment, which is likely to result in nondifferential misclassification of exposure and a consequent bias towards the null hypothesis of no effect. Some inter-study discrepancies may also be attributable to the different age ranges of the study populations, especially since early childhood or *in utero* exposures appear to exert long-lasting effects, which may diminish

over time. Finally...the mean changes observed have generally been of small magnitude and uncertain clinical significance.” (p. 6-44)

The other studies, noted Dr. Witorsch, do not change our assessment of this relationship. Casale *et al.* (1991), in a study of 143 Italian children aged 6-11, found dose-dependent relationships between several measures of lung function, particularly those related to airflow at low lung volumes, and ETS exposure. In this study ETS exposure was measured by both urinary cotinine and parental questionnaire. Goren and Hellman (1995, mentioned on p. 6-38 of the OEHHHA document), in a cross-sectional study of 8,259 Israeli second- and fifth-graders, found no relationship of parental smoking with measures of lung volume and of central or large airway caliber (FVC, FEV₁, PEF, and FEV₁/FVC). Gunesser *et al.* (1994), in a study of 617 Turkish school children (287 boys and 330 girls), aged 9 - 12, found that all measures of lung function were lower in boys exposed to ETS compared with those who were not (with the exception of FEV₁ in 12-year olds), but that these differences were significant only for FVC in 9-year-olds, FEV₁ in 9- and 10-year-olds, peak flow in 10-year-olds, FEF_{25%} in 10-year-olds, FEF_{25-75%} in 9-year-olds. No data were presented for girls. Soyseth *et al.* (1995), in a study of parental smoking and asthma, bronchial hyperresponsiveness, and atopy in 620 Norwegian children aged 7 - 13, reported that, of the 573 children performing spirometry, there was a slight, but not statistically significant decrease in the FEV₁/FVC ratio (one measure of airway obstruction) in relation to maternal smoking (-0.7%), that was even less for paternal smoking (-0.2%). This was the only spirometry result reported in this paper. Cuijpers *et al.* (1995), in a study of 535 Dutch children aged 6-12, found significant decreases in several indices of lung function (FVC, FEV₁, PEF and FEF_{25-75%}) in boys related to cumulative lifetime exposure to ETS, with larger decrements related to exposure during their entire lives versus part of their lives. As with respiratory symptoms, a lesser effect was seen in girls, with only one index (FEF_{25-75%}) showing a similar trend that was significant. Finally, Richards *et al.* (1996), in a cross-sectional study of 395 South African adolescents aged 14-18, found no significant differences in FEV₁ and FEF_{25-75%} between exposed and non-exposed children.

These studies, which were not presented in the OEHHHA report, provide additional evidence on the issue of whether ETS exposure affects lung growth and development, as measured by tests of pulmonary function in children. The reasons for inter-study differences, noted above, apply to these studies as well, particularly problems of misclassification of exposure due to the use of different questionnaires. In this regard, the study by Cook *et al.* (1993) (described on p. 6-42) is instructive. In this investigation of 2,500 English and Welsh school children, aged 5-7, there were significant, consistent relationships between ETS exposure as measured by salivary cotinine and several indices of lung function. These associations were weaker and insignificant when based on questionnaire score, suggesting that this more commonly used method of exposure assessment may well result in a bias towards the null hypothesis.

See also responses to Comment 6 submitted by the Tobacco Institute, below.

3g. Comment and Response – Cystic fibrosis: The commenter notes that a fourth study (Kovesi *et al.* 1993) examining the relationship between ETS exposure and lung function in patients with cystic fibrosis had been published since the appearance of the earlier OEHHA draft. As noted above, this study (as well as a fifth study of ETS and cystic fibrosis – Smyth *et al.* 1994) have been included and discussed extensively on pp. 6-56 and 6-57.

The Tobacco Institute, submitted by Clausen Ely, attorney

Many of the comments submitted by the Tobacco Institute are based on and represent rephrasing of those submitted by Raphael Witorsch, above. Thus, several of OEHHA's responses below reference those above, and vice versa.

1. Comment Summary - Asthma Exacerbation: The commenter references comments submitted by Drs. Philip and Raphael Witorsch on the previous OEHHA draft report in July 1994, and expresses dissatisfaction with OEHHA's response. Specifically, the commenter disagrees that the studies of the relationship of ETS exposure to exacerbation of asthma added to the current OEHHA draft support the conclusion, reached by the U.S. EPA (1992) and concurred with by OEHHA, that there is "sufficient evidence that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease." (p. 6-1 - 6-8) The commenter mentions an additional study potentially relevant to this conclusion (Meinhart *et al.* 1994) and criticizes two discussed by OEHHA (Chilmonczyk *et al.* 1993 and Jindal 1994), and several controlled exposure studies, as evidence contradicting OEHHA's conclusion.

Response: The commenter describes Meinert *et al.* (1994) as reporting "that maternal smoking was associated with a decrease in exercise-induced bronchial responsiveness in asthmatic children 8 years of age." (emphasis in original comment) This report was based on a cross-sectional study of 1401 8-year-old children, of whom 162 were asthmatic, and 92 (of the total) had airway hyperresponsiveness (AHR). The study asked about maternal smoking habits before and during pregnancy, and during the child's 1st and 8th years of life. The investigators found that no mothers of asthmatic children who had AHR (measured at 8 yr of age) began smoking after the child was one year of age, compared with 7.6% of mothers of children with AHR but without asthma, and about 11.5% of mothers of children without AHR. In contrast, 16% of mothers of asthmatic children with AHR quit smoking during this period, compared with 7.6% of mothers of children with AHR but without asthma, and about 3% of mothers of children without AHR. Thus, while the study results appear to represent a decrease in AHR in 8-year-old asthmatic children in relation to maternal smoking, the principal purpose of this paper was to point out that such a superficial reading of the results was an artifact of the mothers' past smoking patterns: mothers with children with AHR, particularly if the children had asthma, were less likely to take up smoking and were more likely to quit during the period preceding the collection of the study data, hence the reference in the title of the article to the "healthy passive smoker."

The commenter focuses on minor inconsistencies in the lung function data in the Chilmonczyk *et al.* (1993) study and on a number of controlled chamber studies with respect to the question of the relationship of asthma exacerbations to ETS exposure. The commenter does not criticize the main finding of the Chilmonczyk study, which was that, whether assessed by urinary cotinine or by parental reporting, ETS exposure in children was found to be associated with frequency of asthma exacerbations in a dose-dependent manner. The study by Jindal (1994) focuses on several indices of morbidity among

asthmatic patients in India, and was cited by OEHHA to the effect that this report suggests that ETS exposure may affect control and severity of asthma in adults as well as children.”(p. 6-6) Exposures and management of asthma are different in India than in California: thus, this suggestion is clearly tentative and indicates the need for examination of this issue in the other societies. In one investigation undertaken among adults residing in Denver, Ostro *et al.* (1994) reported significant effects of both acute and/or chronic exposures to ETS on asthma exacerbations. This is discussed in the OEHHA report (p. 6-8).

The commenter cites several specific controlled exposure studies, the data for all of which are included in the OEHHA report, though the commenter implies otherwise. (The one exception to this is an abstract that was not published as a peer-reviewed report [Musmand JJ *et al.* Tobacco smoke allergy” A fallacy? (abstract) Ann Allergy 1993;70:55].) For example, the commenter states: “Magnussen and coworkers published two studies on the effects of acute exposure to ETS and pulmonary function in asthmatic children (only one of the studies is mentioned in the table of references in the final OEHHA report, and neither is discussed in any detail in the report.) In the first study (1992), acute exposure to ETS (20.5 ppm CO) of ambient air (AA) for one hour produced no significant effect on baseline FEV₁, or specific airway resistance or histamine induced bronchial responsiveness. In the second Magnussen study (1993), ETS exposure produced no significant effect on the exercise-induced bronchoprovocation response.” The second Magnussen study was included in Table 6.2 and noted in section 6.1.1.2 of the OEHHA report. The first Magnussen study contains the exactly the same data on 11 children as reported in greater detail in Oldigs *et al.* (1991), which is included in Table 6.2 and noted in section 6.1.1.2. Thus, including the children’s data from Magnussen (1992) would have resulted in double-counting the same information.

Nevertheless, even if Magnussen (1992) had been included, this would not have altered OEHHA’s conclusions, since these chamber studies, in general, are of limited generalizability. More specifically, “The controlled exposure studies do not clearly demonstrate a consistent effect of acute ETS exposure on asthmatics as a whole...General design constraints in such studies militate against finding effects, *e.g.*, small sample size, systematic exclusion of potential participants who have recently been ill or those with brittle asthma, acute exposures only. Each of these studies has one or more weaknesses in design or analysis; thus, neither individually nor collectively can these investigations definitively address the issue of whether acute ETS exposure can precipitate an asthma flare.” (pp. 6-15 - 6-16) With the exception of Menon *et al.* (1992) OEHHA did not rely on the results of any controlled exposure studies to reach the conclusions articulated above.

2. Comment Summary – Respiratory Infections: The commenter alleges that OEHHA has violated the law (Health & Safety Code Section 39960(c)) by relying on reviews undertaken by other agencies and reiterates comments submitted previously by Drs. Philip and Raphael Witorsch regarding problems with epidemiological studies investigating the relationship between parental smoking and early childhood respiratory

illness. (OEHHA staff have responded to these comments previously (pp. A-22 - A-23)). The commenter also cites several studies that found that maternal smoking during pregnancy appeared to exert a stronger effect on lower respiratory illness in early childhood and lung function in infants and older children (aged 8 - 12), than did post-natal exposure. The commenter acknowledges that these papers are referenced in the OEHHA report, but states that “the significance of these studies and their effect on the prior conclusions of EPA are not discussed by OEHHA in the revised draft.”

Response: It is unclear how the process of producing the OEHHA document violates the law, as alleged by the commenter. Presumably the commenter was referring to Health and Safety Code section 39660(c), describing health effects evaluations for candidate toxic air contaminants, not section 39960(c). However, the OEHHA document is not intended to support regulations under the Toxic Air Contaminants program, even though it will be reviewed by the Scientific Review Panel. Even if this were a regulatory document, there is no explicit proscription against referencing review articles or monographs, such as those produced by the National Research Council or the Surgeon General. The remainder of the content of this comment has already been addressed in the responses to Comment 3b, submitted by Dr. Raphael Witorsch, above.

3. Comment Summary – Otitis Media: Dr. Witorsch's comments filed July 8, 1994 discussed at length the incorrectness of OEHHA's statement in the original draft report... In revising its Report, OEHHA made no attempt to take any of these comments into account. Appendix A contains no response to any of these comments.

Response: As noted below, OEHHA staff responded to Dr. Philip Witorsch's comments in August 1994. Any necessary corrections to the text did take place, (e.g., "In all but three of these 12 studies, statistically significant relationships between exposure and outcome were apparent."), but the responses to comments themselves were inadvertently omitted from Appendix A. We appreciate the Tobacco Institute's pointing out this omission, and it has been corrected.

4. Comment Summary – Asthma Induction: The commenter restates comments submitted previously by Drs. Philip and Raphael Witorsch, as well as those re-submitted by the latter. Please refer to responses to Comment 3.d. of Dr. Witorsch, above.

5. Comment Summary – Chronic Respiratory Symptoms (Children): The commenter does not agree with OEHHA's reliance on the conclusions reached in the three major federal reviews of the evidence that, “a causal relationship is the most likely explanation of the consistently observed associations between ETS exposure and respiratory symptoms in children.” (p. 6-38). As noted in OEHHA's previous response to these comments (pp. A-23 - A-24), rather than re-invent the wheel, the conclusions of the three previous national evaluations of this subject were reviewed by OEHHA staff, and their findings were incorporated in summary form, along with the results of a few more recent studies. The commenter also refers to Dr. Witorsch's most recent “qualitative tally” of such studies, and presents selected results from a few studies (Bråbäck *et al.* 1995, Moyes *et al.* 1995, and Cuijpers *et al.* 1995) as examples of investigations reporting

significant associations with some symptom endpoints in some subpopulations, but not others.

Response: The “vote count” approach of tallying studies that found a statistically significant result versus those that did not is, as noted in the responses to comments submitted by Dr. Witorsch (above), is misleading at best, as it ignores issues related to statistical power, the influence of misclassification of exposure (which typically results in an underestimate of the effect of a given exposure), and other biases. See also responses to Dr. Witorsch’s comments 3.d. and 3.e. The results of dozens of studies, involving tens of thousands of children, served as the basis for the conclusions reached by the National Research Council (1986), the Surgeon General (1986), and the U.S. EPA (1992). Clearly, one would expect some heterogeneity of results among studies examining a variety of symptom endpoints, using different measurement tools, in diverse populations in different parts of the world with different housing conditions and demographics, with varying degrees of statistical power, and using analytic methods that involved adjustment for a variety of confounders and effect modifiers. The studies mentioned by the commenter provide examples of such diversity, but certainly should not be considered as a basis for rejecting the relationships identified between ETS exposure and respiratory symptoms in children. For example, Bråbäck *et al.* (1995) undertook a cross-sectional study of 2,594 children, aged 10-12, in cities in Sweden, Poland, and Estonia, examining a variety of risk factors for respiratory symptoms and for atopic sensitization. The relevant odds ratios, derived from multiple logistic regression analysis, for “coughing attacks” (defined as either nocturnal cough lasting at least 4 weeks or exercise-induced cough) are presented in the following summary:

	All	Sweden	Poland	Estonia
Maternal smoking				
1-9 cigarettes/day	1.55 (1.07-2.24)*	0.67 (0.25-1.78)	1.38 (0.52-3.70)	1.80 (1.15-2.80)**
>9 cigarettes/day	2.60 (1.69-4.01)***	1.40 (0.70-2.80)	2.88 (1.23-6.74)**	4.27 (2.04-8.91)***
* p<0.05, ** p<0.01, *** p<0.001				

There were findings of other significant associations between maternal smoking and respiratory symptom indices in Poland and Estonia, but not Sweden. The difference in results between Sweden and the other two countries may be related to the intensity of smoke exposure related to dwelling size and crowding, since most families in Poland and Estonia lived in apartments, while only about 1/3 of Swedish families did, and the average number of persons per room was 0.9 in Sweden, 1.7 in Poland, and 1.5 in Estonia. In addition, the authors noted that in Sweden there is widespread public awareness of health hazards associated with ETS exposure, leading many parents to smoke outdoors.

Another study cited by the commenter is that of Cuijpers *et al.* (1995), who undertook a cross-sectional examination of a variety of potential indoor environmental influences on respiratory symptoms and lung function in 535 Dutch children, aged 6 - 12. The

commenter cites this study as reporting “statistical significance at 11-20 smokes per day in boys, but not at less than 11 or greater than 20 smokes per day, and no significant association at any dose in girls.” While this statement is true for the analysis of maternal smoking and cough, the numbers of symptomatic boys and girls were small (e.g., 33 and 26, respectively). The “significant” result for 11-20 smokes/day was based on a significance level of 0.10 rather than the more conventional level of 0.05. Examining the symptom of shortness of breath, however Cuijpers *et al.* reported an exposure-response relationship for boys: the odds ratios for <11, 11-20, and >20 smokes/day for maternal smoking were 1.61 (0.58-4.50), 2.80 (1.13-6.95), and 4.58 (1.19-17.65) (again with the significance level set at 0.10, so these represent 90% confidence intervals, which would be even wider had the investigators set $\alpha = 0.05$). While there was no relationship between paternal smoking and boys’ symptoms, the odds ratio for <11 smokes/day for girls was elevated (2.85) and significant at $\alpha = 0.10$. In this study, it appears that boys might be more susceptible to ETS-related effects; however, because the numbers of children affected were so small, the confidence intervals are quite wide.

The third study cited by the commenter, that of Moyes *et al.* (1995) is a cross-sectional investigation of asthma and allergy in 2,614 primary school and 2,752 secondary school children in six districts bordering the Bay of Plenty in New Zealand. They reported that parental ETS exposure was related to nocturnal cough, nasal symptoms, and wheeze in the older (ages 13-14) but not the younger (ages 6-7) children. The odds ratios for nocturnal cough and wheeze were highly significant ($p < 0.01$). While this study does not have the same statistical power issues as that reported by Cuijpers *et al.* (1995), the analysis of passive smoking was quite crude (i.e., “Parental smoking” - yes/no, without stratification by maternal vs. paternal smoking or quantification of numbers smoked/day) and the only other variable adjusted for was ethnicity (European vs. Maori).

The three examples cited by the commenter do show a diversity of results, but considering the differences in the study populations and exposures, statistical power, and methods of analysis, such heterogeneity does not, in OEHHHA’s staff’s opinion, constitute a persuasive basis for rejecting the findings of the prior national reviews and studies published subsequently. Descriptions of these studies will be included in the final OEHHHA report. The limitations of the “vote count” approach to studies reporting statistically significant results versus those that do not have been addressed above.

6. Comment Summary – Lung Development: The commenter states that “OEHHHA’s response to extensive comments [submitted on the previous draft] on the lung development portion of the report is inadequate. It was pointed out at length in the original comments that the longitudinal and cross-sectional studies either relied on in the EPA, NRC and Surgeon General’s Reports, or available at the time the original drafter chapter was issued, did not support a conclusion that childhood exposure to ETS affects lung growth and development as measure by pulmonary function tests.” Though OEHHHA had noted that there were inconsistencies among reports examining these issues, and had modified the report with additional references, the commenter believes that the existing inconsistencies are too substantial to support the conclusions of the EPA, NRC, and

Surgeon General, and OEHHA that ETS exposure is related to small decrements in children's lung function. The commenter then repeats comments submitted previously by Dr. Witorsch, describing inconsistencies in the studies by Sherrill *et al.* (1992) and Lebowitz *et al.* (1992), in support of its position. The commenter also claims that 15 of 17 pulmonary function studies noted in a Table 2 of Dr. Witorsch's current comments were not considered by OEHHA.

Response: These comments echo those of Dr. Witorsch (Comment 3.f., above). As noted above, the current OEHHA draft includes descriptions of at least nine of the 17 studies listed in Witorsch's Table 2 (Lebowitz *et al.* (1992). Sherrill *et al.* (1992), Wang *et al.* (1994), Rona and Chinn (1993), Haby *et al.* (1994), Cook *et al.* (1993), Cunningham *et al.* (1994 and 1995, one of which was not cited by the commenter), Smyth *et al.* (1994) and Kovesi *et al.* (1993). As noted in our prior responses to comments (p. A-24), the relationships of ETS exposure to a variety of lung function measures were extensively reviewed at the federal level and, in order to avoid a duplication of effort, OEHHA staff did not undertake a *de novo* reassessment of dozens of studies, but rather summarized the evidence from the three federal reviews, adding information from the more recent papers noted above. In the view of OEHHA staff, recent evidence generally tends to support the conclusions reached by the national reviews, but suggests that effects on lung growth and development may be attributable in part to persistent influences of maternal smoking during pregnancy. The commenter notes, as does the OEHHA report (pp. 6-43 - 6-44), data on the relationship of ETS exposure to childhood lung function are not consistent. The OEHHA report indicates that the reasons for these inconsistencies "may be explicable by the crudeness of questionnaire-based exposure assessment, which is likely to result in nondifferential misclassification of exposure and a consequent bias towards the null hypothesis of no effect. Some inter-study discrepancies may also be attributable to the different age ranges of the study populations, especially since early childhood or *in utero* exposures appear to exert long-lasting effects, which may diminish over time. Finally...the mean changes observed have generally been of small magnitude and uncertain clinical significance." (p. 6-44)

See also responses to comment 3.f. of Dr. Raphael Witorsch, above.

7. Comment Summary - Cystic fibrosis (CF): Although OEHHA extended the discussion of the relationship of ETS and CF, and modified the conclusion to read to indicate that the "extent and magnitude of such effects are still uncertain," this still overstates the data and the "weight of the evidence." The Kovesi (1993) study found no significant association between parental smoking and several measures of lung function in patients with CF. To fairly summarize the data, OEHHA should have added "that several other studies suggest that children with CF do not experience adverse effects of ETS exposure."

Response: OEHHA staff were only able to identify five published reports examining potential effects of ETS on patients with CF (described on pp. 6-54 - 6-58). The report by Kovesi *et al.* (1993) is discussed extensively, including the lack of a relationship between

parental ETS and lung function in patients with CF. The five studies all examined associations of ETS and lung function in CF patients, with mixed results. It is possible that ETS exposure has no effect on lung function in CF patients, but the lack of consistent findings may be related to the wide range of variability of lung function in this subpopulation, which, combined with the rarity of the disease, makes this outcome difficult to examine. In addition, the limitations related to misclassification of exposure, statistical power, and so forth, noted to affect most studies of ETS and lung function in children without CF, are also applicable here. Three other studies of ETS and CF showed significant associations between ETS exposure and hospitalization for respiratory infection, while two (including the Kovesi study) showed associations with measures of linear growth. In view of the small sample sizes of these studies, the limitations of study design, and the lack of complete concordance among their results, OEHHA staff are still convinced that the conclusion in the document is fair and balanced, i.e., "In summary, although several reports suggest that passive smoke exposure can affect patients with CF, the extent and magnitude of such effects are still uncertain."

RJ Reynolds

James C. Walker for RJ Reynolds

1. Comment Summary: Several references are made to "environmentally realistic" ETS levels, particularly citing a mean figure of "0.7 mg/m³ ETS-RSP" published in Jenkins *et al.* (1996) as a frame-of-reference for smoking-permitted public buildings. Based upon observed ratios of CO (as a surrogate measure) to respirable particles, Dr. Walker concludes that Bascom's group observed their effects at an exposure level "15,000-fold higher than the real-world level."

Response: The above dosimetric calculation is confusing in light of comments from Philip Morris reviewers that observed CO levels in smoking-permitted areas "range from 2.5 in government offices to 13.0 ppm in taverns," (reference: Chappell and Parker, 1977). Given the direct comparability of the exposure measure (CO) and the dramatically smaller margin-of-safety predicted by the study referenced by Philip Morris, OEHHA staff do not agree with Dr. Walker's conclusion that "...the lack of relevance of their [Bascom *et al.*'s] results to human health is quite obvious."

2. Comment Summary: Dr. Walker objects to conflicting terminologies referring to signal transduction in trigeminal irritant chemoreception, including "membrane receptor" and "free nerve endings."

Response: Dr. Walker is correct in asserting that recent work involving the trigeminal response to nicotine stereoisomers indicates the possible existence of specific irritant receptor protein(s), at least for this subclass of compounds. The text has been simplified to eliminate this level of detail.

3. Comment Summary: Dr. Walker made several technical points regarding the sections labeled "exposure dynamics" and "pathophysiology." In response to these comments, several changes/additions were made:

Response: Definitions have been added for "sensory irritation" and "pathological irritation."

The phrase "mucous membrane symptom" has been omitted.

The phrase "sidestream tobacco smoke (STS)" has been substituted for "ETS" in describing studies by Bascom and Willes.

An example has been added of an airborne agent (ammonia) triggering parasympathetic reflexes in the nose (McLean, 1979).

Others

Stanley M Greenfield

Comment Summary (p. 9): The commenter is concerned that the 37 articles included in the meta-analysis of ETS exposure and childhood asthma are inadequately referenced, and therefore could not be identified and reviewed.

Response: The articles used by OEHHA staff in the meta-analysis are indicated by the first authors' last names in Figures 6.1 and 6.2. The full citations for all 37 can be found in the references for Chapter 6.

Otto J. Mueksch

1. Comment Summary: Reports published in the local press attribute decreased lung function in Los Angeles children to air pollution, not ETS. "[A]s you stated correctly, ETS exposure on pulmonary function is likely to be small."

Response: The first part of the comment refers to unreferenced newspaper articles, not scientific publications. The second part of the comment indicates agreement with the OEHHA draft, so no response is necessary.

2. Comment Summary: The commenter notes that smoking prevalence has declined, while the number of children with asthma has increased over the past 20 years, suggesting that "there must be something else responsible for that."

Response: The reasons for the increase in the prevalence of asthma are not entirely clear to the scientific and medical communities. Genetic predisposition, exposure to infectious diseases in early childhood, exposure to specific allergens and to maternal smoking are all considered to be risk factors for the induction of childhood asthma. The comment refers to general social and epidemiological trends, which are subject to the "ecological fallacy" with respect to causal inference. That is, an association (or lack of association) between factors identified at a high level of aggregation (as in this comment) may not hold when studies are done of specific individuals, typically because other important confounding variables are not controlled for at the aggregate level.

3. Comment Summary: I am enclosing an article from the publication of the American Academy of Otolaryngology in 1995, stating that WE FIND THAT THE LITERATURE DOES NOT OFFER SUFFICIENT SUPPORT FOR THE HYPOTHESIS THAT SECOND-HAND SMOKE CAUSES MIDDLE EAR DISEASE TO ACCEPT THE HYPOTHESIS.

Response: The commenter enclosed a single literature review article. In this article, the use of blood or cotinine levels as a surrogate for ETS exposure were considered to be "unusual methods," and hence a design flaw. This position places the authors at the fringe of scientific opinion. Neither of the authors had, themselves, conducted original research on ETS health effects. OEHHA staff respectfully disagree with the conclusions of this review, with the exception of the statement: "The general model of smoke irritating the upper respiratory tract in smokers and, to a lesser extent, passive smokers is not questioned" (Blakley and Blakley, 1995, p. 441).

Claudia Rosa-Bienenfeld

Comment Summary: The commenter is concerned that there have not been studies of effects of smoke or offensive odors that remain on smokers' clothes, hair and so forth after smoking, to which she is very sensitive.

Response: OEHHA staff reviewed published scientific evidence as the basis for the report on ETS. Our review of the literature did not identify any peer-reviewed, published scientific studies that addressed the issue that the commenter raises; therefore, this topic was not covered in the report.

Carol Thompson, Smokers' Rights Action Group

1. Comment Summary: The commenter claims that, "since the anti-smoking movement began, the death rate from asthma has tripled in every age group above five years, while remaining the same in children under five." Therefore, the statements in sections 6.1.1 and 6.2.1, to the effect that ETS exposure can exacerbate asthma and be a risk factor for induction of childhood asthma, are not tenable. Rather, she alleges that the evidence is "more consistent, with more frequent exposure, after age five, to some unknown agent, among sociologically similar smokers and passive smokers than among non-smokers."

Response: The commenter is nearly correct regarding asthma mortality in young children, which increased slightly from 1980-93 (from 1.8 to 1.9 per million population). However, asthma mortality among children aged 5 - 14 doubled from 1980 to 1993 (from 2.5 to 5.2 per million population) (Centers for Disease Control and Prevention, Morbidity and Mortality Weekly 1996;45:350-352). During the period from 1980-1992, hospital admissions for asthma, a somewhat more sensitive indicator of exacerbations, increased substantially for children < age 1 (from 35.6 to 66.3 per 10,000 hospitalizations) and for children ages 1-4 (from 38.3 to 60.1 per 10,000 hospitalizations) (Ibid.). Still, while mortality is a devastating asthma-related outcome, it is relatively rare, and mortality trends are insensitive indicators of asthma prevalence or exacerbations. In addition, the

comment refers to national trends, which are subject to the “ecological fallacy” with respect to causal inference. That is, an association (or lack of association) between factors identified at a high level of aggregation (as in this comment) may not hold when studies are done of specific individuals, typically because other important confounding variables are not controlled for at the aggregate level. Therefore, this comment does not directly address the ETS-asthma issues covered in sections 6.1.1 and 6.2.1 of the OEHHHA report.

2. Comment Summary: The commenter disagrees with OEHHHA’s evaluation of the controlled chamber studies in section 6.1.1.2 and suggests that nonsmokers’ symptoms are due to hyperventilation, which can cause some symptoms that overlap with those reported to be associated with exposure to ETS.

Response: The data that would support this novel suggestion are sparse at best: As the commenter notes, “No studies have ever been done to differentiate the ...symptoms” of hyperventilation from those reported to be due to ETS exposure. Moreover, it is likely that the investigators in the controlled chamber studies (many of whom are physicians) would have been able to recognize whether their subjects were hyperventilating. In addition, hyperventilation is unlikely to cause symptoms of upper respiratory tract and eye irritation or airway hyperreactivity associated with ETS exposure in chamber studies.

3. Comment Summary: The commenter asserts that all studies demonstrating an association between ETS exposure and acute lower respiratory tract illness in children are fatally flawed because they did not control for “touching and hand-washing practices of cases and those with whom they associate. Respiratory infections are not spread by particles in the air, they are spread by physical contact.” Therefore, the conclusions reached by the National Research Council (1986), the U.S. Surgeon General (1986), and the U.S. EPA (1992), upon which OEHHHA relied in its summary of the evidence, are all wrong. “Repeating defective studies over and over again because they serve a political agenda doesn’t make them valid, nor does repeating a lie over and over again make it true.”

Response: The commenter is essentially asserting that: (1) all respiratory illness is due exclusively to hand-to-hand-to-respiratory tract or surface-to-hand-to-respiratory tract transmission; and (2) families in which the parents smoke have poorer hygienic habits than nonsmoking families -- these are the reasons for the higher risk of lower respiratory illness in the younger family members. While scrupulous attention to handwashing could lower the risk of transmission of respiratory illnesses, it is also possible to contract various viral illnesses (e.g., influenza) via inhalation of airborne droplet nuclei generated by coughing, sneezing, or other means from an infected individual in close proximity. Even if the commenter’s statement regarding the necessity for physical contact were true, she provides no evidence that smokers have systematically poorer hygienic practices that might account for the increased risk of lower respiratory tract illness in their children. Therefore, OEHHHA staff disagree with her comments.

4. Comment Summary: We categorically reject this claim [of 78,000-188,000 office visits per year among children under three years of age attributable to ETS exposure] on the grounds that the alleged "risk" is in large part derived from studies of persons at whose age otitis media rarely occurs....there was virtually no "ETS risk" among those under 6 years old.

Response: The attributable risk calculation referenced above utilized relative risk ratio data from Etzel's study, which examined children under the age of 3 years (Etzel et al, 1992). The commenter appears to have confused the attributable risk calculation with the general discussion of ETS and otitis media, as well as having misrepresented the data concerning infants and preschool-aged children. The section is clear on the fact that the increment in OM risk in children occurring as a result of ETS exposure is concentrated in younger children.

5. Comment Summary: The commenter strongly disagrees with the statement in the conclusion in Chapter 6 (p. 6-60) that, although the effect of ETS on lung function in adults is likely to be small, long-term exposure (in combination with other environmental insults) "could contribute to chronic respiratory impairment in adults."

Response: The conclusion referred to by the commenter was based on OEHHA staff review of several reports of chronic respiratory symptoms and conditions in adults discussed in section 6.2.4 (e.g., Leuenberger *et al.* 1994, Robbins *et al.* 1993). The commenter does not directly address these studies or indicate why OEHHA's conclusions are "a gross exaggeration." OEHHA staff believe that the summaries and evaluations of the relevant studies in this report are fair and accurate.

Comment Summaries and Responses on Chapter 7: Carcinogenic Effects Lung Cancer Section

Philip Morris

Philip Morris USA, submitted by Richard Carchman, attorney for Philip Morris

1. Comment Summary: A list of new lung cancer literature is submitted for OEHHA's review and consideration.

Response: OEHHA thanks the commentator for providing this information. Many of the new citations provided consist of non-peer reviewed published meeting proceedings (e.g., articles published in Lung Cancer, volume 14, Supplement 1). Many of the recent peer-reviewed articles noted by the commentator, as well as several of the proceedings papers, have been summarized elsewhere in this Appendix (e.g., see response to Comment # 36 submitted by Mary Ward from RJ Reynolds Tobacco Company, below).

2. Comment Summary: A "List of those Commenting" appears in Appendix A of the Final Draft; this list omits the Comment of Philip Morris U.S.A. on the January 1996 External Review Draft. These comments are resubmitted by Philip Morris U.S.A.

Response: OEHHA regrets that the comments submitted by Philip Morris U.S.A. on the January 1996 Final Draft and OEHHA's responses were inadvertently omitted from Appendix A. These resubmitted comments are discussed below. Many of the issues raised were also made by others commenting, and responses to these issues appear in Appendix A.

3. Comments Summary: In resubmitted comments, Philip Morris asserted that Cal/EPA's review is subjective, selective and unscientific.

Response: OEHHA disagrees with the commentator's characterization of the report. The reader is referred to Comment #18 from Stanley Greenfield, and OEHHA's response for more on the comprehensive and objective nature of the report.

4. Comment Summary: In resubmitted comments Philip Morris asserted that Cal/EPA relies inappropriately on the US EPA risk assessment on ETS, without sufficient attention to the criticisms of that document.

Response: This comment was previously raised by other commentators and considered (See Appendix A, pp. A-26 - A-31). Similar comments were again raised by Dr. Gio Gori (see Comment #15, and response) and others, as discussed elsewhere in this Appendix. With regard to the specific criticism that data from short-term tests and animal experiments were not taken into account by the US EPA, we point out that 1) human data is preferable to animal data and 2) the epidemiologic database for ETS and

lung cancer is unusually rich. Philip Morris submitted, as commentary on the introductory chapter, citations on animal studies, and the reader is referred to the OEHHA response, which includes a discussion of the studies cited.

5. Comment Summary: In resubmitted comments Philip Morris asserted that Cal/EPA's treatment of the epidemiologic data overlooks a number of important issues, including concerns regarding the effects of confounders and bias in the spousal smoking studies, and limited observation of dose-response relationships.

Response: These comments was previously raised by other commentators and considered (See Appendix A, pp. A-26 - A-31). Similar comments were again raised by other commentators as discussed elsewhere in this Appendix.

6. Comment Summary: Philip Morris previously submitted a number of articles related to ETS and lung cancer risk which had been overlooked by OEHHA; a list of these articles is resubmitted by Philip Morris.

Response: OEHHA thanks the commentator for providing this information. Articles with new and relevant information have been reviewed and considered in the preparation of this report.

7. Comment Summary: In resubmitted comments Philip Morris raised procedural issues, and indicated that Cal/EPA should defer from taking any further action on this assessment of risks:

To avoid "bad science", the Cal/EPA report should await the recommendations of the Risk Assessment Advisory Committee;

"It is difficult to see how Cal/EPA would now allow the release of any risk assessment without a determination that the assessment followed the recommendations of the Advisory Committee";

"Cal/EPA cannot take any action based on reliance upon U.S. EPA's Risk Assessment", to avoid the necessary and required original work by Cal/EPA;

"Cal/EPA's ETS risk assessment (and specifically the lung cancer sub chapter) should not be pursued because Cal/EPA lacks the requisite authority to pursue such work";

"Cal/EPA should decline to take any further action on the ETS risk assessment given the extensive regulatory work already underway at the U.S. Occupational Safety and Health Administration (OSHA)."

Response: The report by the Risk Assessment Advisory Committee of our Scientific Advisory Board has been completed. The ETS report is not at variance with recommendations in that report (See responses to general comments ChemRisk submitted). In fact that committee recommended where appropriate that Cal/EPA harmonize assessments with the US EPA. OEHHA has authority to develop health assessments on potential hazards to Californians. The ETS assessment is being

forwarded to the Tobacco Control Section of the California Department of Health Services for its use.

8. Comment Summary: In resubmitted comments Philip Morris indicated that if Cal/EPA does, in fact, elect to continue with the ETS assessment Cal/EPA should:

- 1) Reissue the lung cancer section for review, after taking into account the issues raised in this comment and in any other submissions or workshop testimony received by Cal/EPA;
- 2) Reissue Chapter 7 of the Cal/EPA assessment in its entirety, as the new table of contents indicates some changes from the chapter on “other cancers” issued in May 1994;
- 3) Substantially broaden the scope of its literature review to include all relevant materials, particularly the public record compiled in response to U.S. OSHA’s rulemaking on indoor air quality;
- 4) “Given the unresolved criticisms of the U.S. EPA Risk Assessment on ETS, not rely on that document and its analyses, but obtain the relevant literature and re-analyze it. That is, Cal/EPA must “start from the beginning”, clearly define the criteria used in evaluating data and delineate the rationale for its approaches, in order to reduce the appearance of subjectivity;
- 5) Revise and reissue in draft all other chapters in this assessment of ETS risks, to incorporate the suggestions inherent in the foregoing as to all chapters;
- 6) Review the Congressional Research Service Report, which raised serious questions about the methodology of the U.S. EPA’s ETS risk assessment.

Response: The entire ETS report has been re-released for public comment. The ETS report relies primarily on publications in the scientific peer-reviewed literature. A number of documents submitted to US OSHA were considered in the development of the report. The US EPA document updates reviews of the National Research Council and Surgeon General and reaches similar conclusions. This appendix responds to comments raised on the revised and reissued OEHHA ETS report. The CRS report was considered in the development of this report.

Lawrence B. Gratt, IWG Corp. & Willard R. Chappell, University of Colorado at Denver, for Philip Morris

1. Comment Summary: Gratt and Chappell indicated that previously submitted comments on workplace exposure were not adequately addressed. They had previously submitted a paper “US Worker Lung Cancer Risk From Environmental Tobacco Smoke: Material Health Impairment Unlikely” (Indoor Air ’96 in Nagoya, Japan, July 1996). That paper presents a meta-analysis for workplace exposure: pooled OR=0.99, 90% CI 0.92-1.06. Appendix A response to comments implies that this was not a meta-analysis for US studies only.

Response: We note that in their previously submitted comments, the commentors did not specifically raise issues related to the meta-analysis of workplace exposure studies. Three papers including “US Worker Lung Cancer Risk From Environmental Tobacco Smoke: Material Health Impairment Unlikely” (Indoor Air '96 in Nagoya, Japan, July 1996) were included in the previous submission. The only comment made regarding these submitted papers was that they were “additional information (published and to be published) that we feel may also be useful to Cal/EPA.” The response given in Appendix A was directed at the one published paper presented in June 1995, “Problems with the use of metaanalysis of epidemiological studies in risk assessment: Worker ETS lung cancer risk as an example.”

Regarding meta-analyses of workplace ETS exposure, we refer the reader to the cautionary comments in the OEHHA ETS report (section 7.2.4.2) regarding the difficulties of studying ETS workplace exposures. The indicators of workplace exposure are often limited, for example, to the recent or last job, or at other specific times. In addition to the incomplete assessment of exposure in the workplace in some studies, a major limitation can be the use of surrogate respondents, who may be less able to provide information on the subjects' exposure at the workplace than they are, for example, in the home. Because of these problems meta-analysis of workplace exposure require careful interpretation. In the report on the meta-analysis developed by Dr. Kenneth Brown (*Epidemiological Studies on the Association Between Environmental Tobacco Smoke and Disease: Lung Cancer and Heart Disease*, Meridian Research, Inc., September 1995) most workplace specific risk estimates ranged from 0.91 to 1.40, and Dr. Brown noted “a preponderance of the observed relative risks for lung cancer ... are in the direction of a positive association between workplace exposure to ETS and the occurrence of lung cancer.” Because of the heterogeneity and other factors in workplace ETS studies discussed by Dr. Brown and others we note the difficulty in developing meta-analysis for workplace exposure which provide reliable results.

2. Comment Summary: Drs. Gratt and Chappell commented that OEHHA cited the paper by Janerich *et al.* (1990) for the finding that the highest level of childhood exposure was associated with a statistically significant increased risk of lung cancer, but did not discuss the Janerich *et al.* (1990) findings of a statistically significant decreased risk for exposure to ETS in social settings (OR=0.59, CI=0.43, 0.81).

Response: It is correct that Janerich *et al.* (1990) found a statistically significant decreased risk for exposure to ETS in social settings, however, in reporting their findings, the authors state: “Our assessment of smoking in social settings used an untested, semi-quantitative index in which the case patient or control subject used a score of 0 through 12 to indicate his or her regular exposure to tobacco smoke in social settings during each decade of life. Cumulative lifetime reported scores ranged from nearly 0 to more than 70. The odds ratio from an increase of 20 in the cumulative score was 0.59 (95 percent confidence interval, 0.43 to 0.81).” These investigators acknowledged the uncertainty about this finding, stating: “During the course of this study, regulations in New York began to restrict smoking in the workplace and in social settings such as restaurants. We did not anticipate this development and can not estimate how much the awareness of

these new restrictions might have affected the responses of the study subjects or their surrogates.” Given the authors acknowledged uncertainty about this finding, OEHHA did not believe that it merited discussion.

3. Comment Summary: OEHHA did not discuss the Janerich *et al.* (1990) findings that for workplace exposure, at the equivalent differential of 150 person-years of exposure the odds ratio was 0.91 (CI=0.80, 1.04), i.e., a negative association.

Response: Janerich *et al.* (1990) state: “Estimating the odds ratio as a continuous variable for an equivalent differential of 150 person-years of exposure gave an odds ratio of 0.92 (95 percent confidence interval, 0.80 to 1.04), indicating no evidence of an adverse effect of environmental tobacco smoke in the workplace.” It is difficult to interpret this finding associated with 150 person-years of exposure at work. First, the distribution of ETS exposure at work and the risks associated with different levels of ETS exposure at work were not presented. Second, this level of ETS exposure at work exceeded the highest category of lifetime household ETS exposure (≥ 100 smoker-years of exposure) in table 2 of the Janerich study. Because of the lack of details presented, we concluded (in Table 7.7 of the draft report), as the investigators did, that there was no association between ETS exposure at work and risk of lung cancer but we did not present the point estimate associated with one exposure level at work. Another commenter (A. Judson Wells, see below) provided comments on the Janerich *et al.* (1990) findings for workplace exposure, indicating that the confidence interval is three times too small.

4. Comment Summary: The document frequently makes use of odds ratios greater than one reported at the highest dose even when lower doses have odds ratios less than one.

Response: It is correct that the document discusses and evaluates the results of studies in which odds ratios greater than one are reported at the highest dose, but not at lower doses. In general when using epidemiologic methods, health effects, whether positive or negative, are often detectable only at the higher doses. It is impractical to cite in the text every ORs in the document, since our purpose was to review and synthesize the findings from the various studies. However, the ORs associated with different exposure levels were presented in the specific tables when appropriate. For this reason, we often cited the odds ratios at the highest dose (and not at lower doses), whether the findings were positive or negative. However, we also pointed out, whenever the data were available, whether there was any indication of a trend of increasing risk with increasing levels of exposure or whether the association was present only for certain exposure levels

5. Comment Summary: OEHHA should include the 1995 report by Dr. Kenneth Brown, Epidemiologic Studies on the Association between Environmental Tobacco Smoke and Disease: Lung Cancer and Heart Disease, prepared for Meridian Research, Inc, which updates the EPA meta-analysis to include the new lung cancer studies.

Response: Please refer to page A-27, which briefly discusses the findings of Dr. Brown’s 1995 report and quotes his conclusion that “ETS is a carcinogen”. It is noted that (1) the conclusions of Dr. Brown’s 1995 report have been acknowledged in Appendix A, (2) Dr.

Brown's conclusion that ETS is a carcinogen is consistent with OEHHA's report, (3) the four new lung cancer studies included in Dr. Brown's 1995 report are summarized in OEHHA's report and (4) Dr. Brown's pooled estimate of risk for US studies in Tier I (i.e., "those of greatest utility for investigation a potential association between ETS and lung cancer") is 1.3 (95% CI 1.09, 1.54). The studies in Tier I were released subsequent to US EPA's review.

6. Comment Summary: On page 7-23 there is a statement that Brownson *et al.* (1992) and Kabat and Wynder (1984) limited their indicators of workplace ETS exposure to the most recent or the last job. There is no indication of this in the papers, does OEHHA have other knowledge of this?

Response: Our statement that work ETS exposure was limited to the most recent or the last job was based on the following information presented in these papers. In Table 3 of Kabat and Wynder (1984) there was a footnote that stated that workplace ETS exposure was based on 'current exposure on a regular basis to tobacco smoke at work'. In Brownson *et al.* (1992), these investigators stated that their questions on ETS exposure were partially modeled after those presented in Wynder *et al.* (1985). Based on this sentence, it is difficult to determine how (or which) specific questions were modified from the Wynder *et al.* (1985) study. Data on ETS exposures for 4 jobs were presented in the appendix to Wynder *et al.* (1985).

Thomas B. Starr, ENVIRON International Corporation, for Philip Morris

1. Comment Summary: Dr. Starr agrees with OEHHA that three post-1991 population-based studies of spousal smoking in relation to lung cancer risk have attempted to deal with some of the weaknesses of previous studies, but disputes OEHHA's assertion that these studies "successfully addressed" possible misclassification bias.

Response: The issue of misclassification in the Fontham study is discussed in responses to comments regarding misclassification raised separately by Drs. Tweedie and Dr. LeVois and the reader is referred to these responses for a more detailed discussion. The Fontham study was specifically designed to address the issue of misclassification. To address misclassification of smoking status, Stockwell *et al.* (1992; *JNCI* 84:1417) sought to confirm status at several stages (e.g., when their physician was contacted for permission to interview, at the time of initial contact with the patient or next of kin, at the commencement of the interview). Interview questions sought to elicit in a neutral manner undisclosed tobacco use. Those cases for which smoking status could not be confirmed were excluded.

The issue of misclassification in studies of passive smoking has received considerable attention in the literature. As indicated in two recent publications, this problem is unlikely to explain the positive findings (Riboli *et al.* 1995; *Eur Respir J* 8:285-290; Nyberg *et al.* 1997; *Epidemiology* 8:304-309). Both these studies suggest that to a large extent misclassification of smokers as nonsmokers can be minimized if adequate screening questions are used to ensure that former smokers are identified and are

excluded from studies of lifetime nonsmokers. Although cotinine levels are only a marker of recent tobacco exposure, cotinine measurements are still useful to rule out current smokers. In fact, multiple sources of information and careful screening questions were used in many of the newer ETS and lung cancer studies so that this source of misclassification is being minimized.

2. Comment Summary: Dr. Starr summarizes Dr. Butler's reanalyses of the Fontham *et al.* (1994) data, as presented by Dr. Butler at OEHHA's April 17, 1997 Public Forum (See Comment Summary and Response to Dr. Butler's comments.) He encourages OEHHA to incorporate Dr. Butler's findings in its final document on ETS.

Response: The issue of the Butler reanalysis of the Fontham *et al.* study is provided in detail in the response to Dr. Butler provided below. In summary, the Butler analysis is methodologically problematical, and will not be included in the report.

3. Comment Summary: Dr. Starr suggests that the new studies, while providing additional evidence for an association of ETS and lung cancer, do not establish the causality of this association. He encourages OEHHA to moderate the document's strong conclusions regarding the evidence favoring a causal association between ETS exposure and increased risk of lung cancer.

Response: As discussed in Section 7.2, the OEHHA conclusion is based on previous comprehensive reviews by the U.S. EPA (1992), NRC (1986), and the Surgeon General (U.S. DHHS, 1986) (which each concluded that ETS exposure was causally associated with lung cancer), as well as recent studies reviewed by OEHHA. The National Institute for Occupational Health and Safety also reached similar conclusions (*NIOSH Current Intelligence Bulletin 54*). A careful evaluation of data from 4 studies published since 1991 indicates that these studies, taken together, are consistent with the findings of US EPA, NIOSH, NRC and the Surgeon General's office.

David Sylwester, Department of Statistics, University of Tennessee, for Philip Morris

1. Comment Summary: Establishing a causal link between ETS and lung cancer in humans is difficult, since the epidemiologic data are derived from observational studies, rather than controlled experiments. It is difficult to control for confounding variables in such studies. The work of Lee (1993) suggests that there are lifestyle lung cancer risk factors associated with living with a smoker, which should be considered in any study of ETS and lung cancer. Dr. Sylwester presents an analysis by Lee (1993) of several of these studies, concluding that in most of the studies which showed a large and statistically significant association, the problem of confounding was completely ignored, while the studies which adjusted for these confounders found little or no positive association between ETS and lung cancer.

Response: It is true that not all studies on ETS have evaluated the role of potential confounders, but many of the recent studies, including the largest case-control study

(Fontham *et al.*, 1994) have adjusted for many of the potential confounders. For example, in the Fontham *et al.* (1994) study, the association between ETS exposure and risk of lung cancer was observed after adjustment for various potential confounders including diet, family history of lung cancer, and occupational exposure.

2. Comment Summary: The claim for a causal link between ETS and lung cancer would be strengthened by evidence of a dose-response relationship, however the published data do not support the claim of a dose response effect of ETS on risk of lung cancer since: (1) Brownson *et al.* (1992) report ORs greater than 1.0 only at the highest dose, (2) Janerich *et al.* (1990) show an apparent dose response with smoker years in their Table 2, but the sample sizes are small and the 95% confidence intervals for the odds ratios all include 1.0, implying no association; similar results are seen in other studies [e.g., Fontham *et al.* (1994)], and (3) an observed dose response effect of ETS may be confounded with other risk factors.

Response: Demonstration of a dose-response relationship generally strengthens the evidence for a purported association between a given exposure and risk of a particular disease. However, the fact that not all studies demonstrate a dose-response relationship does not imply there is no association. In the Brownson study (Brownson *et al.*, 1992), an increased risk of lung cancer was present only in the highest ETS exposure group (>40 pack-years of spousal smoking). The Janerich study (Janerich *et al.*, 1992) had small numbers and the effect was small. The Fontham study (Fontham *et al.*, 1994), a substantially larger study than the two mentioned above, found a significant trend of increasing risk with increasing exposure to ETS. In analyses of data in the highest exposure groups, Brown (1995) notes “every one of the 20 individual studies shows increased risk at the highest exposure level, even after adjusting for smoker misclassification”. Further analyses of trends (Brown, 1995) found 9 of 13 studies that reported exposure response data based on cigarettes per day statistically significant at the $p < 0.05$ level.

3. Comment Summary: Meta-analysis of a series of observational studies may yield a very short confidence interval for the effect size, and provide a misleading degree of precision in the results. Caution should be used in interpreting and inferring causality from meta-analyses of ETS/lung cancer studies.

Response: One of the purposes of the meta-analysis is to obtain a more precise point estimate and hopefully a narrower confidence interval for the effect size. We agree that caution should always be used in interpreting and inferring causality from meta-analyses. As discussed in Section 7.2, OEHHA has concluded that ETS exposure is causally associated with lung cancer, based on previous comprehensive reviews by the US EPA (1992), NRC (1986), and the Surgeon General (U.S. DHHS, 1986), and careful evaluation of data published since 1991.

RL Tweedie and MJ Merrilees, for Philip Morris

1. Comment Summary: Previous commentary pointed out that the new studies of spousal exposure to ETS are not really consistent, in the normal sense of the word, either among themselves or with the studies in the EPA Report. The OEHHA response (p. A-30) was that the text had been “modified” to account for this comment. Tweedie found little change to justify this assertion, and noted that the OEHHA document still indicated that “Results from these studies ... are compatible with the US EPA Report” and that “the concordance in these study results gives further credibility to the finding of a causal association between spousal ETS exposure and risk of lung cancer”. “Considerable time is spent, say, explaining away Brownson’s results which are not supportive of the OEHHA thesis. Yet there is uncritical acceptance of the Fontham results which cannot be called concordant with Brownson.”

Response: Brownson *et al.* (1992; *Am J Public Health* 82:1525-1530) note in the conclusion to their study that “Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking.” Among lifetime non-smokers, they report a positive increasing trend in risk with pack years ($p=0.06$). In the highest exposure quartile whether the source was all household members (OR =1.3; 95% CI 1.0, 1.8) or spouses only (OR =1.3; 95% CI 1.0, 1.7) lung cancer risk for lifetime nonsmokers was elevated when the product of pack-years and average number of hours per day was considered. Elevated risk for lifetime nonsmokers was observed in those reporting heavy exposure to passive smoke (OR=1.8; 95% CI 1.1-2.9). Thus, while the findings in the Brownson are not as strongly positive as the Fontham *et al.* study, they do show elevated risk in the highest exposure category for exposure to household or spouse’s smoke

The Fontham *et al.* study, more than other studies to date, took extensive measures to reduce misclassification bias. Information was obtained on each study subject’s personal use of tobacco, first from the medical record of the cancer cases, then from the patient’s personal physician. For those patients whose medical records and physicians did not indicate a history of smoking, the study subject or, if deceased, next of kin was asked about the subject’s tobacco use. Finally, at the time of the in-person interview, a urine sample was collected for cotinine/creatinine analysis. Other strengths of the Fontham study included the small proportion of information on cases from next of kin respondents, complete histological review and control for confounding by a number of suspected risk factors (*i.e.*, age, race, study area, education, a fruit/vegetable/vitamin intake index, dietary cholesterol, family history of lung cancer, employment in high risk occupations). The odds ratio observed for overall exposure to spouse’s smoke is 1.29; the 95% confidence interval (1.04, 1.6) overlaps with that of Brownson *et al.* (0.8, 1.2). In terms of pack-years of exposure from spouses among non-smoking women, Fontham *et al.* report an odds ratio of 1.36 (0.97, 1.91) for 40 - 79.9 pack-years and 1.79 (0.99-3.25) for 80 pack-years and above, and a p-value for trend is 0.03. These are comparable to the findings for 40 or more pack-years of Brownson *et al.*: OR=1.3 (1.0, 1.7), p-value for trend, 0.06.

2. Comment Summary: Tweedie and Merrilees assert that there is publication bias in the ETS studies, and taking this into account, the RR estimate from meta-analyses decreases

to around 1.00-1.10. Since their paper on the topic has now been accepted for publication by the peer reviewed journal *Statistical Science*, Tweedie and Merrilees state that it should be considered as if it were a new paper. The conclusions on publication bias among US studies are, in their view, strong.

Overall Tweedie and colleagues Givens and Smith find that the degree of publication bias is enough to reduce the value for the relative risk for lung cancer associated with spousal exposure to ETS from 1.17 to 1.10. After they take this bias into account they find the relative risk for US studies is no longer significant.

Response: In “Publication Bias in Meta-Analysis: A Bayesian Data-Augmentation Approach to Account for Issues Exemplified in the Passive Smoking Debate” Tweedie and colleagues augment the observations of relative risk in various ETS studies “by simulating the outcomes for the missing studies, thus creating a ‘complete’ dataset for analysis.” To do so they develop a hierarchical Bayesian approach for treating parameters in a standard random effects model of relative risk, and use Gibbs sampling techniques to generate the posterior distribution.

The results of such an approach are dependent on prior distributions. In this case it is assumed that the log RR (logarithm of relative risk) is normally distributed about zero (*i.e.*, a relative risk of unity), that the study variance for each of the individual ETS studies is exactly correct, and that there is a non-trivial probability of publication bias for the least significant class of study (for which p values for individual studies fall between 0.5 and 1).

When the approach and priors are applied to 35 studies on ETS effects in populations inside and outside the US, 22 studies were estimated to be missing, the posterior mean relative risk is 1.14 with 95% posterior probability interval 1.0-1.28, to be compared with a relative risk of 1.22 (1.08, 1.37) when missing studies are not simulated. Application of the approach and priors to 14 US studies of never-smoking females results in an estimate of 4.5 missing studies, and a relative risk estimate of 1.10 (0.95, 1.29). This can be compared to the relative risk estimate of 1.16 (1.04, 1.31) under a random effects analysis and 1.17 (1.02, 1.33) under the Bayesian analysis.

The paper presents an interesting approach for dealing with publication bias, but the criticism that typically arises for Bayesian approaches remains – the subjective judgment used in the selection of priors. For the particular case of the ETS data, sensitivity of the method to priors assumed has been investigated in the paper by Tweedie and colleagues, but for a narrow group of priors and only for the larger meta-analysis which included non-US studies. It would be of interest to see the sensitivity of the results for a wider range of prior assumptions and for the US dataset. The authors have noted that this paper differs substantially from the one previously submitted to OEHHA. We note that the method presented is the same and there are minor differences in the results for the larger dataset application, but that the application to the US studies is new, and the exposition is clearer.

3. Comment Summary: A more appropriate value for the relative risk (RR) associated with spousal ETS exposure, based on taking the new studies into account, is around 1.14-1.16, almost a 25% decrease in the excess risk published in the EPA Report. Tweedie notes that Brown (a co-author of the 1992 EPA Report) calculated a pooled result of 1.09, substantially different than that used implicitly in the OEHHA attributable risk calculations.

Tweedie and Merrilees assert that OEHHA's characterization of their more carefully carried out meta-analyses as "not significantly different from those in the EPA Report" misuses the notion of best estimates. Two papers are pointed out as providing better analyses than used by US EPA -- 1) Mengersen, Tweedie and Biggerstaff (*Australian J Statistics* 37:19-44, 1995) and 2) Tweedie *et al.* (*Lung Cancer* 14 Suppl:171-194, 1996) should have been considered more carefully.

Response: Brown (1995; Epidemiological studies on the association between Environmental Tobacco Smoke and Disease, Meridian Research Inc.) presents a number of risk estimates derived by pooling the results of epidemiological studies through meta-analyses. The estimate derived from US studies without regard to study design (other than sample size) was 1.09 (90% CI=0.99, 1.22). Brown's estimate of relative risk was 1.3 (90% CI=1.09-1.54; $p \leq 0.006$) from Tier I studies, i.e., "studies of greatest utility for investigating a potential between ETS and lung cancer". We note the studies in Tier I were those that took considerable measures to minimize misclassification bias. The papers by Tweedie and colleagues on meta-analyses are of interest, as is the dissertation of his Ph.D. student Biggerstaff. The paper by Mengersen, Tweedie and Biggerstaff is entitled "The impact of method choice on meta-analysis" and addresses choices made in meta-analyses, including the use of fixed versus random effects models, use of unadjusted versus adjusted relative risks, selection of subgroups of studies, use of surrogate data, and accounting for study quality. A number of results of meta-analyses were presented as a means to compare methods. The authors concluded that "Some choices appear to be less important than might have been feared, e.g., the potentially difficult choice between unadjusted and adjusted data seems immaterial in this case, and the use of surrogate data seems to have an overall negligible effect. Also, 'higher quality' studies do not appear to give different results... However, the methods of statistical analysis can lead to noticeably different conclusions... We have shown that there is indeed heterogeneity between studies and that moving to a more appropriate RE [random effects] approach can change point estimates from 1.15 to 1.19 [female case control studies], or from 1.06 to 1.24 [female case control studies using adjusted risks]."

The paper by Tweedie *et al.* published in *Lung Cancer* is a meeting proceedings paper and appears to have been updated by the paper by Tweedie and Merrilees described in the preceding comment and response. The relative risk estimate of 1.16 (1.04, 1.31) was estimated for studies of US females under a random effects analysis and 1.17 (1.02, 1.33) under the Bayesian analysis. Tweedie and colleagues in their various papers develop additional analyses to address publication bias, but as noted in the response to comment 2 above, OEHHA has concerns regarding the assumptions made and methods applied to adjust for the alleged publication bias. In a review funded by the tobacco industry, funnel

plots were found not to indicate publication bias for studies of nonsmoking women in the US (See RJ Reynolds comment and response on the Idle *et al.* study). Also, Tweedie and colleagues in their discussions do not discuss the biases introduced through the ubiquitous exposure to ETS outside the home to presumed unexposed nonsmokers (Riboli *et al.* 1995; *Eur Respir J* 8:285-290).

4. Comment Summary: The existing studies are not as strongly indicative of a causal relationship as the Cal/EPA report claims. Tweedie and Mengersen (*Statistics in Medicine* 14:545-569, 1995) address the existence of a dose-response relationship in the lung cancer-ETS literature. Based on the material in the Draft, it seems far more reasonable to use the heading “suggestive evidence of a causal association” than the stronger assertion for ETS and lung cancer.

Response: The paper by Tweedie and Mengersen evaluates available dose response data by fitting linear and exponential dose response relationships to the individual study data and testing for statistical significance. This is done first including the unexposed and second excluding it for each of the studies with available data. They also conduct meta-analyses of the dose-response data.

When the unexposed are included, and cigarettes smoked per day by the spouse is used as an indicator of exposure, several of the studies show significant increase with exposure under the linear or exponential model. There are fewer cases of significance under the linear model but a review of the test statistics provided indicate that several are of borderline statistical significance; it would have been helpful to have included the p-values for all tests conducted in the tables. The findings when the data for the unexposed are excluded are weaker. To a certain extent this is expected because a large amount of data is discarded by removing the unexposed, making the test for dose response much more conservative. In this case as well there are results that are not marked as significant in the paper, but appear to be of borderline significance upon review of the test statistics provided in the tables for the exponential and linear model fits. Similarly, for the case where spousal exposure is measured in units other than cigarettes per day, significant results, or results of borderline significance, are observed when the unexposed group is included, and the results are weaker when the unexposed are excluded. Overall the findings for the analyses of individual studies are reflected in the meta-analyses performed under corresponding assumptions and data exclusions.

With respect to the 4 studies released since the US EPA report, the largest responses are seen in those most heavily exposed to household smoke. For Stockwell *et al.* (1992; JNCI 84:1417-1422) the dose response for all lifetime household exposures in non-smoking women is reflected in the odds ratios of 1.3 (95% CI 0.6, 2.5), 1.4 (0.7, 2.9), 2.3 (1.1, 4.6) for less than 22, 22-39, and greater than 40 smoke-years respectively. For Brownson *et al.* the finding for 0-15, 15-40 and greater than 40 pack-years was 0.9 (95% CI 0.6, 1.2), 0.9 (0.6, 1.2), and 1.3 (1.0, 1.7), respectively for exposure from all household members and 0.7 (0.5, 1.0), 0.7 (0.5, 1.1) and 1.3 (1.0, 1.7) for exposure from spouses. For the small Kabat *et al.* (1995; *Am J Epidemiol* 142:141-148) study, for female nonsmokers whose spouses smoked 1-10 and more than 11 cigarettes per day, the odds

ratios were 0.82 (0.42, 1.61) and 1.06 (0.49, 2.3); for male nonsmokers the corresponding results were 0.74 (0.24, 2.23) and 7.48 (1.35, 41.36). Finally for Fontham *et al.* (1994), the results in terms of less than 15, 15-39.9, 40-79.9, and over 80 pack-years of exposure were 1.08 (0.86, 1.39), 1.04 (0.76, 1.42), 1.36 (0.97, 1.91), 1.79 (0.99, 3.5), respectively. These studies suggest increasing response with increasing exposure. As noted above, because of the extensive effort to address misclassification of smoking and disease status, and control for confounders, the study by Fontham *et al.* is viewed as a very strong study. The study “is considered by [US] EPA to be the best designed study on secondhand smoke and lung cancer conducted to date.” (US EPA, 1994; *Setting the Record Straight: Secondhand Smoke is a Preventable Health Risk*, EPA 402-F-94-005). The study by Stockwell *et al.* also carefully addressed the misclassification issue through the methodology employed to determine smoking status.

With respect to the issue of causality, the meta-analysis performed by US EPA is one of the findings of previous reviews that was considered. Indeed, US EPA (1994 cited above) notes that their “finding that secondhand smoke is a known cause of lung cancer in humans is based on all the evidence ... If the meta-analysis were removed from the report entirely, the findings would be precisely the same.” Similarly the 1986 *Report of the Surgeon General* found after weighing the evidence that “the data presented in this report establish that a substantial number of the lung cancer deaths that occur among nonsmokers can be attributed to involuntary smoking.” The 1986 National Research Council Report *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects* also concludes that “Considering the evidence as a whole, exposure to ETS increases the risk of lung cancer in nonsmokers.” OEHHA in reviewing the available evidence, including that presented in the reports by the NRC, US EPA and in the 1986 *Report of the Surgeon General* concluded on the weight of the evidence that ETS exposure causes lung cancer in nonsmokers.

5. Comment Summary: Tweedie states that the OEHHA Review Draft is unresponsive to comments he made on the previous draft regarding workplace exposures. In previously commenting Tweedie submitted a publication by himself and others entitled “Passive smoking in the workplace: classical and Bayesian meta-analyses” by Biggerstaff, Tweedie and Mengersen (*Int Arch Occup Environ Health* 66:269-277,).

Response: The nature of the initial criticism of the report made by Tweedie is still unclear. The paper cited finds nonsignificantly elevated relative risks for male nonsmokers exposed to ETS in the workplace under meta-analyses using classical and (empirical and full) Bayesian approaches. The authors indicate that because of the extensive variability among the male studies there should be concern about combining results, noting that the heterogeneity observed may be due to covariates not included in the model. For the analysis of workplace exposure in nonsmoking females, they note that the several methods they use did not lead to different conclusions. They noted “there is for females a raised point estimate of excess risk of the order 5%-10%, and this is not significant...In all this analysis we have deliberately ignored any need to adjust for cofactors in the population.”

The OEHHA report is careful to point out the limitations of the workplace exposure studies, but notes that the studies with more complete evaluation of workplace exposure are generally supportive of an association. The OEHHA report does not provide estimates of risks from exposure in the workplace.

The Tobacco Institute

The Tobacco Institute, submitted by Clausen Ely of Covington and Burling, attorneys for The Tobacco Institute

1. Comment Summary: OEHHA did not adequately address the comments submitted by Drs. Gori, Layard, LeVois, and James Wilson. Comments previously submitted are summarized here:

- a). Differences between ETS and Mainstream Smoke were not taken into account; the average ETS-exposed individual is exposed to much lower levels of respirable particulates than the active smoker;
- b). OEHHA did not address the inadequacies of the US EPA report, on the sole basis that the EPA report had undergone peer-review, and that its conclusions were “consistent with other authoritative reviews by the National Research Council and the Surgeon General.” OEHHA ignores the critique of the EPA report by the US Congressional Research Service (CRS) (Gravelle and Zimmerman, 1994; Redhead and Rowberg, 1995);
- c). The published studies are inconsistent and bias and confounding factors in those studies were not taken into account;
- d). OEHHA wrongly asserts that later studies remedied the problems with earlier studies and are compatible with a causal association between ETS and lung cancer, while ignoring the critiques of these recent studies by Drs. Gori, LeVois, Layard and others (e.g., Butler);
- e). OEHHA failed to conduct its own independent assessment of the relevant scientific evidence. Under California Health and Safety Code § 39960(c), OEHHA must critically review all relevant scientific data, and can not rely on the 1992 EPA Report as the basis for its assessment of any ETS/lung cancer risk. OEHHA’s response to this comment in Appendix A misconstrues the Advisory Committee’s recommendation that Cal/EPA harmonize its risk assessments with federal EPA, and ignores OEHHA’s statutory duty;
- f). OEHHA’s heavy reliance on the Fontham study and Dr. Butler’s serious questions about that study’s conclusions indicate that OEHHA should obtain and evaluate the original data of the Fontham study.

Response: Many of these comments, which were previously raised, considered and addressed in Appendix A by OEHHA, have been raised again by other individuals, and are discussed elsewhere in this Appendix. Additional specific responses to some of the above points follow:

- a) The co-authors of the US EPA 1992 report have commented extensively on this issue, and have pointed out numerous flaws in Gori's characterization of the relative exposure of tobacco smoke components in ETS-exposed individuals and in active smokers (Jinot and Bayard, J Clin Epidemiol 47:339-349, 1994).
- e) OEHHA respectfully disagrees with the commentator.
- f) Dr. Butler's concerns about the Fontham study have been addressed elsewhere in this Appendix.

2. Comment Summary: OEHHA made no changes of substance to the draft chapter in response to any of the comments.

Response: OEHHA gave careful consideration to all comments received, and made changes to the report when warranted.

3. Comment Summary: OEHHA did not produce a balanced assessment of the frequently conflicting scientific studies.

Response: OEHHA disagrees with the commentator's characterization of the report. The reader is referred to Comment #18 from Stanley Greenfield [#1], and OEHHA's response for more on the objective nature of the report.

Gio Batta Gori, The Health Policy Center, for The Tobacco Institute

1. Comment Summary: The draft accepts the 1992 US EPA report on ETS at face value and states that studies published after the 1992 report (1) are compatible with a causal association of ETS and lung cancer and (2) support the reports of the US EPA, the Surgeon General and the National Research Council of 1986.

Response: As stated in Appendix A, page A-28, in our response to a previous comment by Dr. Gori, "the U.S. EPA analysis underwent extensive public scrutiny and external scientific peer review, and the general conclusions reached regarding the relationship between lung cancer and exposure to ETS are consistent with other authoritative reviews by the National Research Council and the Surgeon General." As discussed in Section 7.2, OEHHA has concluded that ETS exposure is causally associated with lung cancer, based on previous comprehensive reviews by the U.S. EPA (1992), NRC (1986) and the Surgeon General (U.S. DHHS, 1986), and careful evaluation of data published since 1991. The recent studies published after 1991 do support the three earlier reviews and taken together do provide additional evidence that ETS exposure is causally associated with lung cancer. (For additional information, please see responses #3 and #4 to Comment #18 from Stanley M. Greenfield.)

2. Comment Summary: The draft states that the latest studies successfully addressed many of the weaknesses of the earlier studies. This statement implies that the earlier reports by the EPA, the Surgeon General and the National Research Council were flawed since they were based on the earlier studies.

Response: The earlier reports by the EPA, the Surgeon General and the National Research Council were comprehensive well-conducted analyses, which concluded that ETS exposure was causally associated with lung cancer, based on the total weight of evidence. Most of the individual studies included in these three earlier analyses found a small increased risk, and a few found statistically significant results; however, all the studies published in the 1980s had small sample sizes which limited statistical power to detect small associations. The fact that the more recent studies successfully addressed many of the weaknesses of the earlier studies, such as small sample size, in no way detracts from the earlier analyses of the EPA, the Surgeon General and the National Research Council.

3. Comment Summary: It is incorrect to state, as the draft does, that “Each of the three population-based studies show a statistically significant increase of lung cancer risk.”

Response: This is addressed by response #3 to Comment #18 from Stanley M. Greenfield.

4. Comment Summary: The Stockwell and Brownson studies do not mention the problem of misclassification, and the Fontham study uses an incredibly low misclassification adjuster, based on cotinine levels.

Response: Stockwell *et al.* and Fontham *et al.* focused on minimizing misclassification in designing their studies. In the Stockwell and Fontham studies, the definition of lifetime nonsmokers was limited to individuals who had smoked less than 100 cigarettes and had no more than 6 months of tobacco use in their lifetime. Both of these studies used multiple sources of information (i.e., medical records, physicians’ offices, at the time of contact to set up the interview, and at the beginning of the interview) to verify the lifetime nonsmokers’ status. In addition, the Fontham study corroborated subjects’ current nonsmoking status by measurement of urinary cotinine. Urine samples were collected and interviews conducted in the home or another location selected by the subjects, but not in the hospital (See response to Comment #30 from A. Judson Wells). Fontham *et al.* (1994) excluded cases and controls whose cotinine/creatinine concentration exceeded 100 ng/mg (2 of 365 (0.6%) of cases and 25 of 1064 controls (2.3%)). In addition, there were 9 cases (2.5%) and 29 controls (2.7%) who had cotinine/creatinine concentrations of 55 to 99 ng/mg. The ETS-related risk estimates were obtained with and without excluding this group of 38 subjects. There was no overall difference in the study findings between their two analyses.

5. Comment Summary: If a misclassification rate of 3% is assumed, then none of the recent studies would have a positive finding. This level of misclassification is justified, based on the data presented in Figure 2.1 of the draft.

Response: The US EPA took into account bias of all kinds, including that due to smoker misclassification, by adjusting each study separately for this, before performing any further analyses on the data. The US EPA used a misclassification rate specific for each

study, and, in the case of the Fontham study, calculated different rates for current and former smokers. The studies conducted prior to 1992 were varied in the vigor in which nonsmoking status was checked and confirmed. Stockwell *et al.* and Fontham *et al.* were very aware of the concern of misclassification of smokers as nonsmokers and were very vigorous in ruling out smokers.

[After his presentation at the forum, in response to a question from a member of the SRP, Dr. Gori stated that none of his comments represented any new information, but were restatements of previously submitted comments.]

6. Comment Summary: At the April 1997 public forum Dr. Gori stated that none of the studies conducted to date are statistically significant at the 95% level of confidence.

Response: This is not true. Please see the response to Comment #18 from Stanley M. Greenfield, which enumerates several of the results from the Brownson, Stockwell, and Fontham studies that are statistically significant at the 95% level of confidence.

7. Comment Summary: At the public forum Dr. Gori stated that there are several reports that the misclassification rate in many studies is quite high for smoking status.

Response: The US EPA carefully addressed the smoker misclassification issue in its 1992 report, and found that the misclassification rates differed from study to study, dependent on study design and execution. Table B-3 of Appendix B in the 1992 US EPA report presents data from the analysis of bias in seven studies, and suggests that the average misclassification rate for *these particular studies* is on the order of 3%. OEHHA notes that the studies conducted since 1991 were well aware of the problem of smoker misclassification, and were designed to minimize such bias, particularly the Fontham *et al.* study. Two recent studies (Riboli *et al.* 1995; *Eur Respir J* 8:285-290; Nyberg *et al.* 1997; *Epidemiology* 8:304-309), using different methodologies, conclude that while there is some misclassification of smokers as nonsmokers, the misclassification rate is low and is unlikely to explain the lung cancer risk from ETS exposure. Both studies suggest that to a large extent misclassification of smokers as nonsmokers can be minimized if adequate screening questions are used to identify former smokers and if cotinine measurements can be used to identify current smokers. Multiple sources of information to mitigate against smoker misclassification are used in the better recent studies.

8. Comment Summary: At the public forum Dr. Gori stated that several other risk factors have been identified for lung cancer (e.g., milk intake, low vegetable intake, beer drinking, cooking methods), yet virtually all the studies have not adequately controlled for confounding factors such as these.

Response: Well designed epidemiological studies of ETS exposure and lung cancer pay particular attention to the problem of confounding. As summarized in Section 7.2.3, the U.S. multicenter study (Fontham *et al.*, 1994) and a study conducted in Greece (Kalandidi *et al.*, 1990) found little evidence of confounding by dietary factors (including intake of fruits and vegetables, supplemental vitamin use, and dietary cholesterol). Several other

factors including employment in high-risk occupations (Fontham *et al.*, 1994) and previous lung diseases (Brownson *et al.*, 1992; Wu *et al.*, 1995) were examined and found not to confound the association of ETS exposure and lung cancer.

9. Comment Summary: At the April 1997 public forum Dr. Gori stated that the draft should state explicitly which calculations led to the statement on page 7-25 that “The consistency of the findings in the four recent studies and the meta-analysis results of the US EPA indicate about a 20% increase of lung cancer risk in nonsmokers.”

Response: This discussion is already in the report (Section 7.2.3 in the Final Draft, Section 7.2.4 in the final document).

Maurice LeVois, Environmental Health Resources, for The Tobacco Institute

As part of his comment Dr. LeVois submitted a paper authored by himself and Paul Switzer entitled: “Differential exposure misclassification in case-control studies of environmental tobacco smoke and lung cancer.”

1. Comment Summary: The report claims that the ETS/lung cancer data are consistent, but it is not clear how the consistency of the results was assessed.

Response: The reader is referred to Section 7.2.3 of the draft report (Section 7.2.4 in the final document).

2. Comment Summary: The report is wrong to claim that the four “recent” ETS/lung cancer studies are consistent with the US EPA meta-analysis, since the Brownson study is null.

Response: Brownson *et al.* (1992; *Am J Public Health* 82:1525-1530) note otherwise: “Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking.” Among lifetime non-smokers, they report a positive increasing trend in risk with pack years ($p=0.06$). In the highest exposure quartile whether the source was all household members (OR =1.3; 95% CI 1.0, 1.8) or spouses only (OR =1.3; 95% CI 1.0, 1.7) lung cancer risk for lifetime nonsmokers was elevated when the product of pack-years and average number of hours per day was considered. Elevated risk for lifetime nonsmokers was observed in those reporting heavy exposure to passive smoke (OR=1.8; 95% CI 1.1-2.9). Thus, while the findings in the Brownson study are not as strongly positive as the Fontham *et al.* study, they do show elevated risk in the highest exposure category for exposure to household or spouse’s smoke.

3. Comment Summary: The slightly elevated risk in the highest exposure group is accompanied by a reduction in risk in the lowest positive exposure group in both the Brownson and the Fontham studies, and is consistent with the effects of recall bias. “The Fontham study does not discuss exposure misclassification and no adjustments for such misclassification were made...” (p. 23, LeVois and Switzer). Differential

misclassification of only a few percent can produce statistically significant observed trend distributions in the absence of any true effect.

Response: The overall dose response data for the 4 studies is presented in Table 7.5. The study of Brownson *et al.* does indicate a lower odds ratios in the lower exposure categories, but beyond providing hypothetical examples of how it might occur, LeVois provides no additional evidence to support their contention that this is due to misclassification bias.

The adjusted odds ratios for the Fontham *et al.* data are 1.0, 1.08, 1.04, 1.39 and 1.79 for the following groups: unexposed, less than 15, 15.9 to 39.9, 40 to 79.9 and 80 pack-years of exposure to spouse's smoke, respectively. For the case of self-respondents exposed to multiple sources of exposures, the odds ratios are 1.0, 0.79, 1.20, 1.44, 1.67 for 0, 1-11, 12-28, 29-47, and ≥ 48 adult smoke years of exposure, respectively. The trend test p value associated with this finding is 0.0006. The 95% confidence interval associated with the odds ratio lower than one in the lowest exposure group is (0.44, 1.42), far from significantly less than one. This is the finding that LeVois and Switzer point to as the evidence for misclassification bias in the Fontham *et al.* study. Regarding whether or not Fontham *et al.* discuss misclassification bias, this was a primary focus in study design: a subject's personal use of tobacco was obtained from medical records of the cancer cases, from the patient's personal physician, from the study subject, through a questionnaire at the screening phase, and during the in-person interview. A second matched control group of women diagnosed with primary cancer of the colon was selected also as a means of assessing recall or response bias associated with recent diagnosis of cancer or with being ill. There is an extensive discussion of misclassification bias with respect to study findings in the "comment section" of the Fontham *et al.* publication. Riboli *et al.* (1995; *Eur Respir J* 8:285-290) and Nyberg *et al.* (1997; *Epidemiology* 8:304-309) provide evidence indicating that for studies less well designed than this one, the positive findings are unlikely to be due to misclassification bias.

4. Comment Summary: 1) The inconsistency of the urinary cotinine results of the Fontham study are indicative of misclassification bias. 2) Figure 2.1 suggests that the smoking distribution is bimodal, and that about 17% of the self-reported nonsmokers are deceivers, an order of magnitude more than considered by US EPA.

Response: Regarding the first point, Fontham found 0.6% of 53.5% of the cases and 2.3% of 83.3% of the controls to have cotinine/creatinine concentrations of 100 ng/mg or higher and excluded them to eliminate persons likely to be active smokers. The greater proportion found in the controls is likely to be due to the extensive screening of cases done because of concerns over misclassifying as nonsmokers lung cancer cases. Applying the same rates and logic to the remainder of the cases and controls whose urinary cotinine was not sampled suggests that 0.4% of non-smoking controls and 0.3% of cases were likely to be smokers. Thus the procedure used by Fontham *et al.* reduced misclassification to levels where the level in controls and cases differed slightly, with the level in controls slightly higher than that of the cases. Higher rates of smokers in the

controls biases the findings toward the null hypothesis; in this case the bias is unlikely to be strong since rates in the controls appear to be very low.

The Fontham *et al.* study was designed specifically to reduce misclassification, both intentional and that due to recall bias. Because misclassification of cases that are smokers as nonsmokers is a particular concern, Fontham *et al.* went to considerable lengths to reduce that type of misclassification. Information was obtained on each study subject's personal use of tobacco, first from the medical record of the cancer cases, then from the patient's personal physician. For those patients whose medical records and physicians did not indicate a history of smoking the study subject or, if deceased, next of kin was asked about the subject's tobacco use. At the time of the in-person interview, a urine sample was collected for cotinine/creatinine analysis. Regarding classification of disease status, 100% of the cases in the Fontham *et al.* study were histologically confirmed. For 85% an independent second review of the already histologically confirmed diagnosis was conducted, the main purpose being to determine the concordance on histologic classification between community pathologist versus one (the study) pathologist.

Regarding the second point of LeVois, the cotinine/creatinine measurements in the study of Fontham, discussed above, indicates that in studies well designed to address the issue, misclassification can be minimized.

5. Comment Summary: If the recent studies by Stockwell, Brownson, Fontham, Kabat and Cardenas are included in a meta-analysis with the older studies, the U.S. female summary relative risk is 1.08 (95% CI 0.97-1.20; 90% CI 0.99-1.18).

Response: Details on the meta-analysis were not provided by Dr. LeVois. We note that focusing on the US studies on ETS exposure in nonsmoking women identified as high quality studies (Tier I) would result in a significant and substantially larger value (e.g., 1.3; see Brown 1995). We caution that over-adjustment for misclassification bias in meta-analyses can substantially reduce results. Dr. LeVois believes misclassification rates to be larger than US EPA and some other researchers. As noted in the recent study by Riboli *et al.* (1995) "the potential upward bias in the relative disease risks which may be due to smoker misclassification is counterbalanced by the downward bias from background ETS exposure among the supposedly unexposed group".

6. Comment Summary: The Cardenas *et al.* (1997) paper is not reviewed in the draft report. Cardenas *et al.* do not find a statistically significant increased risk of lung cancer death associated with ETS, however the authors noted that their study had very low statistical power as a result of the relatively small number of lung cancer deaths in the study population. Results of the Cardenas study are inconsistent when analyzed using different definitions of ETS exposure, and estimated ETS exposure is based upon very limited smoking information.

Response: The Cardenas *et al.* (1997) report has been added to the document. These investigators found that among women, those married to husbands who ever smoked showed a 20% (RR 1.2; 95% CI=0.8-1.6) increased risk compared to women married to

never-smokers after adjustment for age, race, diet, and occupation. The risks increased with increasing numbers of cigarettes smoked by husbands (RRs were 1.0, 1.1, 1.2, and 1.9 for 0, 1-19, 20-39, 40+ cigarettes per day, respectively) (p for trend = 0.03) and with increasing pack-years of exposure (RRs were 1.0, 1.0, 1.5, and 1.5 for 0, 1-16, 17-35, and 36+ pack-years, respectively) (p for trend = 0.1). In both nonsmoking women and nonsmoking men, there was no association between risk of lung cancer and hours of ETS exposure per year. However, Cardenas *et al.* (1997) cautioned that information on hours of exposure per day was much less complete and the missing data on self-reported ETS could have resulted in misclassification and thus biased the study findings toward an absence of effect.

7. Comment Summary: Calculation of a combined sex relative risk of 1.19 for the Kabat study is meaningless and misleading. Kabat *et al.* report male and female results separately, and conclude that the study is null; the draft report misrepresents this study as supportive of an ETS/lung cancer association.

Response: A clarification has been added to the report regarding the study of Kabat *et al.* The Kabat *et al.* study is a study of low power. Elevated odds ratios for exposed vs unexposed are observed for males and females whose spouses smoked, but the elevation is not statistically significant. The ETS report provides this information. The largest odds ratios are observed for the most heavily exposed, and the finding is statistically significant for the males (OR 7.48, 95% CI 1.35, 41.36). OEHHHA agrees that because of limitations in study design and size, the Kabat *et al.* study contributes little to the overall evidence.

8. Comment Summary: The five newer studies are consistent with an absence of risk, and do not support the inference of causality. Adding the data from studies published since the EPA report, the US female ETS/lung cancer risk estimate has declined over time, and is not statistically significant.

Response: The discussion on lung cancer in the report (section 7.2), and the discussion of the Cardenas study in response to the 6th comment summary above and in response to the RJ Reynolds submission provides an alternative viewpoint.

9. Comment Summary: At the April 1997 public forum Dr. LeVois stated that there is not enough detail provided concerning what the weight-of-the-evidence methodology is. The report does say that sample size is considered in the weight-of-the-evidence approach. If so, then OEHHHA should perform an evaluation of the adequacy of the sample size of the epidemiologic studies. For lung cancer, if one takes a level of association of 1.3, and calculates what sample size is needed, at a given significance level and power level then one will conclude that the lung cancer studies are not large enough to test the hypothesis.

Response: Some additional detail regarding weight of evidence has been added to Chapter 1. Regarding information about the uncertainty of the results and study power,

inspection of confidence intervals provides the necessary information, as noted by Dr. Friedman of the SRP during the April 1997 public forum.

10. Comment Summary: In evaluating the weight-of-the-evidence, OEHHA should also provide a more complete discussion of confounding. Dr. LeVois suggests listing the potential confounders reported in the literature. The report does list some of the confounders considered, but it doesn't compare that to anything; it is unclear how OEHHA weighed the evidence. LeVois notes that his own data indicate that smoking and non-smoking households differ. Smoking households are more run down, have more unemployed people, are more overcrowded. It is impossible to tell if the studies adequately addressed and properly adjusted for confounders.

Response: The discussion of confounding has been expanded (Section 7.2.3). The better studies consider confounding due to socioeconomic factors of the type noted by Dr. LeVois.

11. Comment Summary: Bero *et al.* are cited as an adequate study of publication bias, however, LeVois disagrees, pointing to his own work (LeVois and Layard) which indicates that there is a preference for publishing positive associations. The draft ignored comments submitted previously that the failure of researchers to publish (1) dose response results and (2) probably null workplace data are forms of publication bias.

Response: In response to previous public comment, a discussion of publication bias was added, citing both Bero *et al.* and LeVois and Layard, as well as other papers. While publication bias regarding publication of dose response data is asserted, no evidence of this has been provided. Regarding failures to publish negative studies, there have been a number of publications examining the so-called funnel plot, which looks at the pattern of relative risk estimates as a function of study size, or standard error of the estimate. A recent document sponsored by the tobacco industry evaluated the extent of publication bias by examining funnel plots (*Environmental Tobacco Smoke and Lung Cancer: An Evaluation of the Risks, Report of a European Working Group*; see discussion of Idle *et al.* below in response to comments submitted by RJ Reynolds). For workplace exposure the Working Group concluded the "the pattern of points gives no reason not to accept that the points are a random sample from all possible studies ..." Similarly, publication bias was not noted for studies of childhood exposure. For spousal smoking studies, regional differences were noted and the group found "no evidence of publication or any other study size related bias" for the US studies. The group did speculate that lack of dose response data reporting in some studies may be due to publication bias, but they did not evaluate this issue systematically.

Others

Stanley M. Greenfield

1. Comment Summary: In general, this comprehensive report is unbiased and objective, however, there are several instances where a bias towards the hypothesis of an adverse ETS impact are evident. Example: The summary of the Brownson *et al.* (1992) lung cancer study.

Response: We disagree with the commentator's characterization of the summary of Brownson *et al.* (1992) as biased.

2. Comment Summary: Exposure to ambient air pollution and specifically particulates must be treated as an important confounder in any epidemiology study of ETS. Without offering any supporting evidence, OEHHA states that this was "carefully considered in the analysis".

Response: A confounder is defined as an additional variable that is itself associated both with the factor and with the disease. Major sources of air pollution include motor vehicle exhausts, residential and commercial space heating, oil- and coal-fired power plants, industrial emissions, and farming activities. OEHHA is aware of the evidence suggesting a correlation between exposure to certain components of air pollution and increased risk of disease. With regard to lung cancer, the relationship with air pollution has been difficult to study, particularly in western countries, and the relative risk appears to be small. The strongest associations are evident from studies conducted in China where the conditions are quite different than in the U.S. Thus, in most studies of ETS and lung cancer conducted in western countries, it is questionable whether particulates will be an important confounder.

3. Comment Summary: The report incorrectly states that the three recent population-based lung cancer studies show statistically significant effects associated with long term ETS exposure.

Response: We disagree that the statement is incorrect. Statistically significant effects were reported by Stockwell *et al.* (1992) for adult exposure to ≥ 40 smoke-years of household ETS (2.5, 95% CI=1.1-4.6), for adult exposure to ≥ 40 smoke-years of spousal ETS (2.2, 95% CI=1.0-4.9), for childhood/adolescence exposure to ≥ 22 smoke-years of household ETS (2.4, 95% CI=1.1-5.4), for combined childhood/adolescence and adult exposure to ≥ 40 smoke-years of household ETS (versus ≤ 22 smoke-years) (2.3, 95% CI=1.1-4.6). Statistically significant effects were reported by Brownson *et al.* (1992) for exposure to ≥ 40 cigarette pack-years of spousal ETS (1.3, 95% CI=1.0-1.7). Statistically significant effects were reported by Fontham *et al.* (1994) for ever exposed to spousal smoking (1.29, 95% CI=1.04-1.60), for ever exposed at the workplace (1.39, 95% CI=1.11-1.74), for workplace exposure of ≥ 31 years (1.86, 95% CI=1.24-2.78), and for adult exposure to ≥ 48 years from all sources (1.74, 95% CI=1.14-2.65).

4. Comment Summary: The report concludes that the new studies are "consistent" or "comparable" with the EPA 1992 report, but a more recent meta-analysis by Brown indicates that the new studies show less of an effect than the EPA 1992 pooled estimate.

Response: The three recent population-based lung cancer studies included in Brown's most recent meta-analysis do show statistically significant effects associated with long term ETS exposure (see response #3 above), and thus are consistent with the EPA 1992 report. Brown, in conducting meta-analyses of the ETS exposure and lung cancer, evaluated studies on the basis of study quality and sorted them into tiers, as was done in the US EPA ETS document. (*Epidemiological Studies on the Association Between Environmental Tobacco Smoke and Disease: Lung Cancer and Heart Disease*, Meridian Research, Inc., September 1995). Brown reported pooled results for studies of nonsmokers in various countries for studies of similar quality. For US studies in "Tier 1", corresponding to studies judged to be of highest quality, Brown reported a pooled relative risk estimate of 1.3 ($p = 0.006$). The Fontham *et al.* and Stockwell *et al.* studies were the ones placed in this group. These studies were designed to minimize misclassification. Thus from this new set of studies, once study quality is taken into account, a somewhat higher value is suggested.

Otto J. Mueksch

Comment Summary: The commentator provides information which seems to have been left out of OEHHA's search, in preparing the report on ETS. He submits an overview of a report issued by the Congressional Research Service (CRS) on Nov. 14, 1995, *ETS and Lung Cancer Risk*. The CRS report is more recent than other sources quoted in OEHHA's report. As summarized in the overview, A). In May 1994 CRS stated in testimony before a Senate Committee that the "statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking"; B). The CRS 11/14/95 document, "Environmental Tobacco Smoke and Lung Cancer Risk" raises various issues about the EPA and OSHA reports.

Response: OEHHA did consider the CRS report, *Environmental Tobacco Smoke and Lung Cancer Risk* in developing the ETS report..

Carol Thompson, Smokers' Rights Action Group

Comment Summary: A causal link between ETS and lung cancer has not been established. Ms. Thompson suggests that "previous lung disease" may be an important confounder in the ETS/lung cancer studies, mentions *Chlamydia pneumoniae* as a possible etiologic agent of concern, and provides notes on the association of lung cancer with previous lung disease, drawn from selected epidemiology literature.

Response: The US EPA (1993), the National Research Council (1986), the Surgeon General (U.S. DHHS, 1986), and OEHHA have concluded that ETS is causally associated with lung cancer, based on the weight of the evidence. With regard to the potential for previous lung disease to act as a confounding variable, studies which have examined this possibility (e.g., Brownson *et al.*, 1992; Wu *et al.*, 1995; Fontham *et al.*, 1994) did not find any evidence for confounding of the association of ETS exposure and lung cancer (See Section 7.2.3).

A. Judson Wells

1. Comment Summary: With regard to the discussion of smoker misclassification, the draft does not mention Table B-3 of Appendix B in the 1992 EPA report. This table summarizes data from seven studies, and provides valuable guidance for taking into account smoker misclassification. In addition, Drs. Wells, Perez-Stable, Wagenknecht and English have submitted a paper for publication which presents new data showing that smoker misclassification has only a minor effect on the relative risk of lung cancer from passive smoking.

Response: OEHHA thanks the commentator for this information. A discussion of two recent studies addressing the issue of smoker misclassification (i.e., Riboli *et al.*, 1995, and Nyberg *et al.*, 1997) has been added to the document (See Section 7.0). For additional comments on the US EPA's consideration of misclassification in the US EPA 1992 report, please see response #5 to Comment #15 from Gio Gori.

2. Comment Summary: In Chapter 7, page 1, reference should be made to my discussion of compounds in the vapor phase of ETS, Environ Int 1991;17:382-385, in addition to Guerin *et al.*

Response: OEHHA thanks the commentator for this information. The reference has not been included in the document, however, since it provides information supplemental to that already discussed in Chapter 2, Exposure Measurements and Prevalence.

3. Comment Summary: In 7.2.2 there is one new lung cancer/passive smoking study missing, namely, Schwartz *et al.* Am J Epidemiol 1996;144:554-562. Their OR for home exposure is 1.1 (95% CI, 0.8-1.6) and for workplace 1.5 (95% CI, 1.0-2.2).

Response: This new study by Schwarz *et al.* (1996) has been added to the document..

4. Comment Summary: Re page 7-16 on Brownson *et al.* (1992) there is some evidence that subjects who said they were not exposed and those who said they were only lightly exposed may have been mixed. If those exposed up to 50 pack years x hours per day in Table 2 are used as the reference category, then the results are in better agreement with other studies, i.e., the crude ORs increase for 'exposure from all household members' (1.14) and for 'spouse only exposure' (1.11). Similarly, if the '0 to 24 smoker years of exposure' group is used as the reference category for the Janerich *et al.* (1990) study, the crude OR for total household exposure increases to 1.30.

Response: Since exposure is ubiquitous, it is difficult to determine a baseline group who did not have any ETS exposure. The objective is, in fact, to compare the risk of those with very high levels of ETS exposure and those with very low or no exposure. Thus, it is quite plausible that those in the no exposure and next lowest exposure category both have low levels of ETS exposure and that the risk estimates are apparent when these two groups with low exposures are combined.

5. Comment Summary: Re the Fontham *et al.* study (1991, 1994), it has been claimed that the cotinine measurements on the cases don't mean much because the measurements

were made in hospital where smoking wasn't allowed. In fact, Dr. Fontham has said that all of the interviews and urine samples of cases and controls were done in the subjects' homes.

Response: For more information on this issue, please see A. Judson Wells' follow-up comments (i.e., Comment #30 and OEHHA's response).

6. Comment Summary: Provides a series of comments relevant to the interpretation of workplace meta-analyses sponsored by the tobacco industry: (1) Re 7.2.4.2 and Table 7.7 on workplace exposure, the confidence intervals for Garfinkel *et al.* (1985) are incorrect; the correct workplace 95% CI's are 0.88 (0.46-1.67) and 0.93 (0.55-1.55). Meta-analyses conducted with the incorrect data may overweight these low ORs by a factor of five. (2) The workplace result from Janerich *et al.* (1990), namely 0.91 (95% CI, 0.80-1.04), is in error, the confidence interval is three times too small; it was also derived from a linear regression, and thus is not appropriate for incorporation into a meta-analysis. Meta-analyses conducted with the incorrect data are overweighted about nine times. (3) The workplace result for non-smokers in Wu-Williams *et al.* (1990) appears in the paper as 1.1, but the correct OR, as shown in Table 7.7, is 1.2.

Response: OEHHA thanks the commentator for providing this information.

7. Comment Summary: Suggest adding (1) the workplace results for passive smoking and lung cancer from the theses by Butler T (1988) and Jackson (1989) and (2) the study by Schwartz *et al.* (1996) to the discussion in 7.2.4.2 and to Table 7.7

Response: Only peer reviewed studies published since 1991 on the association of ETS and lung cancer were summarized in the document. However, a brief summary of the published study by Schwartz *et al.* (1996) has been added to the document..

A. Judson Wells

1. Comment Summary: Submits a letter from Steven Bayard, Ph.D., EPA Project Manager, ETS Risk Assessment, to A. Judson Wells, Ph.D., which addresses issues of recall bias and smoker classification in the Fontham study. The letter reports a conversation with Dr. Fontham, to the effect that (1) none of the interviews of cancer cases were conducted in hospital, and (2) the data from the first three years of her study, published in 1991 and reporting results of two separate control groups (colon cancer cases, and population-based), do not indicate that cancer cases demonstrated recall bias regarding exposure to ETS.

Response: OEHHA thanks the commentator for this information. Additional information from the authors of the Fontham study follows: Almost all the interviews in the Fontham study were conducted in the homes (or a location selected by the subjects, but not while they were in the hospital). During the first three years of the study, colon cancer patients were interviewed as a second group of controls. Differential recall

between lung cancer cases and colon cancer controls should be minimized since both groups are similarly motivated to recall earlier exposures (Fontham *et al.*, 1991).

RJ Reynolds Tobacco Company

RJ Reynolds Tobacco Company, submitted by Mary Ward

1. Comment Summary: Since the Cal/EPA document on ETS exposure and lung cancer was released in January 1996, publications have become available “that Cal/EPA must consider as it revises Chapter 7 of the 1997 draft”: The company notes that as a result the analysis contained in Chapter 7 of the 1997 draft is incomplete and uninformed by important new findings.

Publication	Issue raised by RJ Reynolds (RJR)
1. Cardenas <i>et al.</i> (1997) Environmental tobacco smoke and lung cancer mortality in the American Cancer Society’s Prevention Study II. <i>Cancer Causes Control</i> 8:57-64; Cardenas (1995). Ph.D. dissertation, Emory University.	RJR notes that the two documents analyze the American Cancer Society Cancer Prevention Study II (CPS II) and find that the risk of lung cancer attributable to ETS is not statistically significant. “These results are consistent with other evidence submitted by RJ Reynolds on this issue and are inconsistent with the conclusions reached by Cal/EPA.” RJR extracts from the Cardenas 1995 and 1997 analysis. RJR notes that Cardenas <i>et al.</i> (1997) “abandoned the long-standing statistical principle that non-significant results do not indicate an association.” RJR also makes several comments on the similarities and differences between the two publications.
2. Idle <i>et al.</i> (April 1996). <i>Report of a European Working Group. Environmental Tobacco Smoke and Lung Cancer: An Evaluation of the Risk.</i>	<ol style="list-style-type: none"> “Idle <i>et al.</i> analyze 48 epidemiological studies related to ETS and conclude that ETS is not a primary lung carcinogen.” “The Idle <i>et al.</i> analysis is inconsistent with US EPA conclusions”; US EPA failed to consider numerous sources of bias and confounding in spousal epidemiologic studies; A meta-analysis is inappropriate when the studies are heterogeneous; Fonham <i>et al.</i>’s treatment of smoking status misclassification elevates the observed risk estimate; The inability to control for bias and confounding is a major weakness of epidemiological studies; Diet is a critical confounding factor that must be examined in studies of ETS and lung cancer; A trend test is not a dose response test; Publication bias is evident in the ETS literature.
3. Sterling <i>et al.</i> (1996). An alternative explanation for the elevated mortality and morbidity risks association with exposure to ETS. <i>J Clin Epid</i> 49:803-808.	“Sterling <i>et al.</i> address socioeconomic status and paraoccupational exposure as confounders in the studies on ETS, morbidity and mortality: ‘Insofar as industrial and other blue collar workers are now likely to bring home toxic materials on their person, and also are more likely to smoke than those in other occupations, members of a household are much more likely to be subject to a paraoccupational exposure and belong to lower socioeconomic strata if the household contains a smoker than if the household does not contain a smoker.’” Observations of effects may be due to differences in paraoccupational exposure or socioeconomic strata.
4. Nilsson (1996). Environmental Tobacco Smoke and Lung Cancer: A Reappraisal. <i>Ecotoxicology and Environmental Safety</i> 34: 2-7.	<ol style="list-style-type: none"> There are histological inconsistencies among the tumors reported in the epidemiological studies that undermine the confidence in the reported risks. Confounder in the Fonham study: There was a greater percentage of persons of lower socioeconomic status among the cases compared to the controls; diet was not addressed <p>misclassification resulted from recall bias during interviews and from use of surrogates for deceased subjects. It is a mistake to assume that cotinine measurements are sufficiently accurate to mitigate against misclassification in the range of 5-10%</p>
5. Law and Hackshaw (1996). Environmental Tobacco Smoke <i>British Medical Bulletin</i> 52:22-34.	RJR finds that these authors “superficially review the ETS literature in what appears to be a search for evidence to support a claim of detrimental effects from ETS exposure.” “They projected a ETS relative risk of 1.2 on Wald’s 1984 work... then assume, based on ETS studies published through early 1994, and not on original data of their own, that worldwide ETS studies can be combined into a single meta-analyzed estimate of 1.24. This estimate has little value for Cal/EPA because it is not based on US studies...” RJR further note that they “also conjecture self-servingly regarding confounding and bias. They dismiss dietary confounding by citing older epidemiology studies and found no change in risk.”
6. Delamothe (1996). Whose data are they anyway? <i>British Medical</i>	“RJR submits this article to Cal/EPA as further evidence that Cal/EPA should obtain and make available to all interested parties the raw data from the study by Fonham et

<i>Journal</i> 312:1261-1262.	al...The requests for Fontham raw data are consistent with established scientific principles. Epidemiological societies encourage sharing data so that research findings are replicated..."
Publication	Issue raised by RJ Reynolds (RJR)
7. Moolgavkar and Luebeck (1996). A critical Review of the evidence on particulate air pollution and mortality. <i>Epidemiology</i> 7:420-428.	RJR notes the relevance of the Moolgavkar and Luebeck findings for air pollution, who note a. "the main problem faced by the meta-analyst can be summed up in one word: heterogeneity" b. "confounding is by far the most important issue in epidemiological studies, such as those of air pollution in which relative risks are small."
8. Wynder (1996) Response to Science article, <i>Epidemiology</i> faces its limits <i>Am J Epi</i> 8:747-749; Gori (1996). Epidemiology, risk assessment and public policy <i>Risk Analysis</i> 16:291-293.	RJR notes that Gori addresses the uncertainty inherent in weak statistical associations by quoting "[l]oose judgmental criteria have been introduced to give causal appearance to statistical associations: strength, consistency, specificity, temporality, response gradient, plausibility, coherence, and analogy. Such criteria are inadequate for an analytical evaluation of how uncertain causal inferences might be, and they fail to address the structural uncertainties derived from biases and confounders." RJR also quotes from Wynder "[t]rue associations of this order [less than 2.0] are more likely to be affected by classification biases, confounding, case or control selection, and selective subgroup analysis than would be the case for large order associations." RJR goes on to note that "Because it is uncontroverted in the record that all of the studies on ETS, lung cancer and heart disease produce, at most, 'weak associations, Cal/EPA must carefully apply the principles discussed by Gori and Wynder in interpreting these issues."
9. Biggerstaff (1995). <i>Random Effects Methods in Meta-Analysis with Application in Epidemiology</i> . Ph.D. dissertation, Department of Statistics, Colorado State University, Fort Collins	RJR in commenting on this dissertation states that "According to Biggerstaff, sensitivity analysis mandates that the authors of a study check the accuracy of all of their assumptions." RJR states that "Biggerstaff explains that the classical 'logit' analysis, the type of analysis used in the epidemiology studies relied on by both US EPA and Cal/EPA, under-estimates the confidence interval (CI) width by 5-10% compared to a Fisher exact CI". RJR states that "This issue was not considered further in Biggerstaff's analyses nor was it considered in the Cal/EPA analyses. Thus, Cal/EPA's reliance on logit analyses increases the likelihood that the agency's assumptions regarding ETS and lung cancer are not as stable as they appear to be." In discussing the results of Biggerstaff's application of the methodology to ETS RJR states that "Biggerstaff's analysis should be accorded no weight by Cal/EPA" because it does not account for publication bias, possible effects of other biases such as misclassification of smoking status, or confounding.
10. Lee and Forey (1996). Misclassification of smoking habits as a source of bias in the study of Environmental Tobacco Smoke and Lung Cancer. <i>Statistics in Medicine</i> 15:581-605.	RJR emphasizes the following points in submitting this paper: a. When the magnitude of an association is weak, addressing misclassification bias is critical b. Misclassification biases may lead to an apparent relationship when no true relationship exists c. The US EPA report underestimates the impact of bias due to smoking status misclassification d. The Wells model that is the basis of the US EPA's misclassification adjustment is unreliable e. The misclassification rates used by US EPA are too low.
11. Schwartz <i>et al.</i> (1996). Familial risk of lung cancer among nonsmokers and their relatives. <i>Am J Epidemiol</i> 144:544-562.	RJR notes that Schwartz <i>et al.</i> report an association between lung cancer in nonsmokers and family history of lung cancer, and provide evidence that family history is a potential confounder for studies attempting to analyze ETS and lung cancer. RJR notes that the risk estimates provided by this study for ETS exposure at home (OR 1.1, 95% CI 0.8-1.6) and work (OR 1.5, 95% CI 1.0-2.2), while adjusted for age, sex and race, are not adjusted for other factors identified in the paper.

Response: We appreciate the submission of copies of the original documents by RJ Reynolds. This facilitates our review of the comments submitted. Following the order of submission, in the discussion below OEHHA addresses the points raised by RJR in these publications.

Publication	Issue Raised by RJR
1. Cardenas <i>et al.</i> (1997) Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Prevention Study II. <i>Cancer Causes Control</i> 8:57-64; Cardenas (1995). Ph.D. dissertation, Emory University.	RJR notes that the two documents analyze the American Cancer Society Cancer Prevention Study II (CPS II) and find that the risk of lung cancer attributable to ETS is not statistically significant. "These results are consistent with other evidence submitted by RJ Reynolds on this issue and are inconsistent with the conclusions reached by Cal/EPA." RJR extracts from the Cardenas 1995 and 1997 analysis. RJR notes that Cardenas <i>et al.</i> (1997) "abandoned the long-standing statistical principle that non-significant results do not indicate an association." RJR also makes several comments on the similarities and differences between the two publications.

Contrary to the commenter's suggestion, we believe that the findings of Cardenas (1995) and Cardenas and coworkers (1997) are not inconsistent with the findings presented in the Cal/EPA 1997 final draft report, which support an increased lung cancer risk of 20% among nonsmoking women with husbands who smoke. The Cardenas *et al.* (1997) report has been added to the final document. The analysis by Cardenas *et al.* (1997) utilized data from the American Cancer Society CPS II study which included approximately 1.2 million subjects who were enrolled in 1982. This analysis was based on 7 years of follow-up of the cohort. The main analysis was based on 247 lung cancer deaths (150 females, 97 males) in 288,776 nonsmokers (192,234 females, 96,542 males). Among women, those married to husbands who ever smoked showed a 20% (RR 1.2; 95% CI=0.8-1.6) increased risk compared to women married to never-smokers after adjustment for age, race, diet, and occupation. The risks increased with increasing numbers of cigarettes smoked by husbands (RRs were 1.0, 1.1, 1.2, and 1.9 for 0, 1-19, 20-39, 40+ cigarettes per day, respectively) (p for trend = 0.03) and with increasing pack-years of exposure (RRs were 1.0, 1.0, 1.5, and 1.5 for 0, 1-16, 17-35, and 36+ pack-years, respectively) (p for trend = 0.1). Although there was not a smooth trend of increasing risk with increasing years in marriage to a smoker, all the RRs were above 1.0 (RRs were 1.0, 1.5, 1.5, and 1.1 for 0, 1-17, 18-29, and 30+ years in marriage to smoker) (p for trend = 0.5). Among nonsmoking men, those married to wives who ever smoked showed a RR of 1.1 (95% CI=0.6-1.8) compared to men married to wives who never smoked.

A second analysis utilized self-reported data on current ETS exposure (any exposure or total hours of exposure). In both nonsmoking women and nonsmoking men, there was no association between risk of lung cancer and hours of ETS exposure per year. However, Cardenas *et al.* (1997) cautioned that information on hours of exposure per day was much less complete and the missing data on self-reported ETS could have resulted in misclassification and thus biased the study findings toward an absent [absence] of effect.

As a matter of background Dr. Cardenas was supported in his graduate research by scholarships from Emory University and the WK Kellogg Foundation.

Publication	Issues raised by RJR
2. Idle <i>et al.</i> (April 1996). <i>Report of a European Working Group. Environmental Tobacco Smoke and Lung Cancer: An Evaluation of the Risk.</i>	<ul style="list-style-type: none"> a. “Idle <i>et al.</i> analyze 48 epidemiological studies related to ETS and conclude that ETS is not a primary lung carcinogen.” “The Idle <i>et al.</i> analysis is inconsistent with US EPA conclusions”; b. US EPA failed to consider numerous sources of bias and confounding in spousal epidemiologic studies; c. A meta-analysis is inappropriate when the studies are heterogeneous; d. Fontham <i>et al.</i>’s treatment of smoking status misclassification elevates the observed risk estimate; e. The inability to control for bias and confounding is a major weakness of epidemiological studies; f. Diet is a critical confounding factor that must be examined in studies of ETS and lung cancer; g. A trend test is not a dose response test; h. Publication bias is evident in the ETS literature.

RJR states that the Idle *et al.* analysis is inconsistent with the US EPA’s conclusions, as the group analyzed 48 epidemiological studies and concluded that ETS is not a primary lung carcinogen. Idle *et al.* found the studies of spousal exposure to ETS and lung cancer “erratic and contradictory”. The consistent finding of effect in more highly exposed groups in individual studies was not considered in the evaluation by Idle *et al.* US EPA has noted that the largest increases in effect have been observed in all of the studies on spousal exposure they reviewed for which risks by exposure levels were evaluated. In the studies published since the US EPA review and included in the Cal/EPA report, the largest risks were also observed in those most exposed to spousal smoke. This same pattern emerges in the recent peer reviewed publications evaluating risks at different exposure levels -- Cardenas *et al.* (1997; *Cancer Causes and Control* 8:57-64) in terms of cigarettes smoked per day by spouse and Liu *et al.* (1993; *Am J Epidemiol* 137:145-54).

With respect to US EPA consideration of misclassification bias, the Idle *et al.* discussion of misclassification bias focuses on smoking wives of smokers being classified as nonsmokers. Riboli *et al.* (1995; *Eur Respir J* 8:285-290) reported on a collaborative study regarding misclassification of smoking status in ETS epidemiological studies using urinary cotinine as a biomarker. They found that, based on cotinine measurements, roughly 1.5% of the subjects identifying themselves as non-smokers may in fact be smokers. They concluded that “potential bias due to smoker misclassification is very unlikely to be responsible for the increased health risks observed in the epidemiological studies,” and stressed that “because exposure to ETS is so widespread, the potential upward bias in the relative disease risks which may be due to smoker misclassification is counterbalanced by the downward bias from background ETS exposure among supposedly unexposed groups.” Nyberg *et al.* (1997; *Epidemiology* 8:304-309) studied misclassification in two large cohorts using information on smoking obtained several years apart. They found that misclassification of smokers mainly concerns light smokers or long time ex-smokers, “who have only very moderately elevated risk of lung cancer”... “implying that smoker misclassification bias does not explain the lung cancer risk from ETS exposure.”

With respect to confounders, Idle *et al.* stress the importance of dietary contributions to cancer risk. Many of the more recent studies have addressed many of the potential confounders. For example, Fontham *et al.* (1994) included among other factors diet, family history, and occupational exposure in their analyses of ETS impacts; Cardenas *et al.* adjusted for age, race, education, dietary consumption of vegetables and total fat, asbestos exposure, blue collar employment, and history of chronic lung disease. Further, increased risks are consistently observed in studies from different countries which vary by lifestyle factors, including diet. The observation of greatest increases in risk in the most highly exposed, along with the consistency of evidence across a variety of cultures makes it unlikely that confounding can explain these findings.

Idle *et al.* note “the special methods used by Fontham *et al.* 1994 to eliminate misclassified smokers involved testing subject’s urine for cotinine and eliminating those whose cotinine level suggested that they were a smoker. Perversely, this special care to remove current smokers may have increased the bias. This arises because a lower proportion of the cases than the controls were tested and thus more of the misclassified controls than the misclassified cases were detected and removed.” Fontham *et al.* analyzed urine samples for 356 (53.5%) of 665 cases and 1064 (83.3%) of 1278 controls. The difference in the proportions of cases and controls is attributable to deceased cases. A high proportion of living study subjects were able and willing to provide a urine sample, and the proportions were similar for self-reported cases (81.1%) and controls (83.3%) despite differences in health status. An analysis only focusing on the self-reported cases found significantly increased risks. Further, Fontham found 0.6% of 53.5% of the cases and 2.3% of 83.3% of the controls to have cotinine/creatinine concentrations of 100 ng/mg or higher and excluded them to eliminate persons likely to be active smokers. Applying the same rates and logic to the remainder of the cases and controls whose urinary cotinine was not sampled suggests that 0.4% of non-smoking controls and 0.3% of cases were likely to be smokers. Thus, the procedure used by Fontham *et al.* reduced misclassification to levels where the level in controls and cases differed slightly, with the level in controls slightly higher than that of the cases.

With respect to heterogeneity in meta-analyses, Idle *et al.*’s position is somewhat unclear. While as RJR indicates, Idle *et al.* state that meta-analysis works only if studies “are unbiased as a group and are homogeneous” Idle *et al.* perform meta-analyses and form conclusions on the basis of their meta-analyses of studies which they recognize not to be homogeneous (*e.g.*, page 52). We note that OEHHA did not conduct a meta-analysis of the lung cancer and ETS exposure studies, but did report the result of US EPA’s meta-analysis. US EPA conducted a tiered analysis to address the issue of heterogeneity. OEHHA notes that the finding of a causal association between ETS exposure and lung cancer by the US EPA, US Surgeon General and National Research Council did not turn on results of meta-analyses.

RJR asserts that the Idle *et al.* analysis supports publication bias. However, in the funnel plot analyses conducted by Idle *et al.* for workplace, childhood and spousal exposure studies publication bias was not evident. They did state that it can not be ruled out for non-US studies of spousal smoking solely because outside the US the small studies

constituted a large proportion of the total studies. "...although publication bias does not appear to be operating for studies on US populations (see earlier), it may exist for studies in the rest of the world. It cannot be ruled out that the study size dependence in the non-US studies may reflect the relative sizes of the studies from various regions in the world and the variation in the Asian studies already noted." RJR stated that Idle *et al.* found "publication bias was evident" and this is hardly the case.

With respect to the statement that a trend test is not a dose response test, OEHHA notes that significant positive trends reflect increasing risk with exposure, and this is indicative of a dose response relationship. Further discussion of this issue is provided in response to Drs. Tweedie and Merrilee's comment #4.

As a matter of background, Idle *et al.* (identified in their report as "the European Working Group") was sponsored by Philip Morris Europe SA, British American Tobacco Company Limited, and Rothmans International Services Limited. A rebuttal to the report has been produced by Sanner (Norwegian Radium Hospital), Dybing (Norwegian Institute of Public Health), Repace (contributor to US EPA document), and Vainio (International Agency for Research on Cancer), but only the summary of the rebuttal was available to OEHHA.

Publication	Issues raised by RJR
3. Sterling <i>et al.</i> (1996). An alternative explanation for the elevated mortality and morbidity risks association with exposure to ETS. <i>J Clin Epid</i> 49:803-808.	"Sterling <i>et al.</i> address socioeconomic status and paraoccupational exposure as confounders in the studies on ETS, morbidity and mortality: 'Insofar as industrial and other blue collar workers are now likely to bring home toxic materials on their person, and also are more likely to smoke than those in other occupations, members of a household are much more likely to be subject to a paraoccupational exposure and belong to lower socioeconomic strata if the household contains a smoker than if the household does not contain a smoker.'" Observations of effects may be due to differences in paraoccupational exposure or socioeconomic strata.

Sterling *et al.* offer as "an alternative explanation" for the association that "observed differences in risk of mortality or morbidity ascribed to ETS on the basis of a comparison of households with and without smokers may be partly or entirely due to differences in paraoccupational exposure and socioeconomic strata." As evidence they provide seven observations: 1) occupation and socioeconomic factors are associated with smoking patterns; 2) paternal and spousal occupation and disease are linked; 3) possible exposure to carcinogens brought home by parents and spouses from the workplace; 4) association between socioeconomic level and mortality; 5) significant risk for nonsmoking females of smoking husbands is reported, but not in general for nonsmoking males of smoking wives; 6) studies of lung cancer and workplace exposures are inconclusive; 7) healthier lifestyles of wives married to nonsmokers.

With respect to the observations regarding socioeconomic factors, the case control studies considered by US EPA which included socioeconomic factors as the basis for matching cases and control showed elevated risks associated with ETS exposure. More recently,

the studies of Fontham *et al.* and Cardenas *et al.*, which controlled for a variety of factors related to socioeconomic status, were consistent with a finding of overall increased risk due to ETS exposure of roughly 1.2; increases in risks in the more heavily exposed were greater. For the 5th observation above, Sterling *et al.* note that “The fact that significantly elevated risk is limited to female nonsmoking spouses and children of smokers supports the presence of factors other than or in addition to ETS.” Factors for non-smoking men that tend to bias findings toward the null include the potential for greater exposure to ETS among those identified as “unexposed”, the potential for greater occupational exposure to carcinogens, the possibility of greater misclassification (see e.g., Nyberg *et al.* 1997; *Epidemiology* 8:304-309), and the potential for over-adjustment where ETS and certain occupational exposures interact to induce the effect. This also applies to workplace exposures (6th observation above). We note the argument made by Nilsson *et al.* regarding histological inconsistency between cancers associated with ETS and with occupational carcinogens is contradictory with the argument by Sterling *et al.*

As a matter of background the Sterling *et al.* research was supported by a grant from the British Tobacco Company.

Publication	Issue raised by RJR
4. Nilsson (1996). Environmental Tobacco Smoke and Lung Cancer: A Reappraisal. <i>Ecotoxicology and Environmental Safety</i> 34: 2- 7.	a. There are histological inconsistencies among the tumors reported in the epidemiological studies that undermine the confidence in the reported risks. b. Confounder in the Fontham study: There was a greater percentage of persons of lower socioeconomic status among the cases compared to the controls; diet was not addressed c. In epidemiological studies of ETS, misclassification results from recall bias during interviews and from use of surrogates for deceased subjects. It is a mistake to assume that cotinine measurements are sufficiently accurate to mitigate against misclassification in the range of 5-10%

Regarding point a, because “all established human lung carcinogens, including inorganic arsenic, ..., as well as mainstream tobacco smoke, seem preferentially to induce tumors of the Kreyberg type I”, and because the proportion of adenocarcinomas is small compared to squamous cell and small oat cell carcinomas in tobacco induced cancer in smokers, Nilsson finds that the histological findings are inconsistent, since the strongest findings for passive smoking are with adenocarcinomas.

We agree that, while active smoking does increase lung adenocarcinoma, it does cause greater increases in squamous cell and small cell carcinoma. Also, there is a striking association between lung adenocarcinoma and ETS exposure (Fontham *et al.*, 1994), although association between ETS and other histological types of lung cancer are also observed. Differences in the physical and chemical properties of ETS compared with smoke drawn into the lung by the active smoker include the distribution of vapor and particulate phase components and of identified carcinogens.

There are also differences in inhalation, with nasal versus oral inhalation perhaps yielding a greater fraction of peripheral adenocarcinomas in the ETS exposed.

With respect to dietary and socioeconomic confounders in the Fontham *et al.* (1994) study, the analysis adjusted for: education; race; fruits, vegetables, supplemental vitamins index; dietary cholesterol; employment in high risk occupations; family history of lung cancer; age.

Regarding misclassification bias, while present, it does not appear to explain the relationship between ETS exposure and lung cancer, as noted in recent studies on the subject by Nyberg *et al.* (1997; *Epidemiology* 8:304-309), and Riboli *et al.* (1995; *Eur Respir J* 8:285-290). The discussion above of these studies in regard to this issue will not be repeated here.

The sponsorship of Prof. Nilsson's work is not indicated in the publication.

Publication	Issue raised by RJR
5. Law and Hackshaw (1996). Environmental Tobacco Smoke <i>British Medical Bulletin</i> 52:22-34.	RJR finds that these authors "superficially review the ETS literature in what appears to be a search for evidence to support a claim of detrimental effects from ETS exposure." "They projected a ETS relative risk of 1.2 on Wald's 1984 work... then assume, based on ETS studies published through early 1994, and not on original data of their own, that worldwide ETS studies can be combined into a single meta-analyzed estimate of 1.24. This estimate has little value for Cal/EPA because it is not based on US studies..." RJR further note that they "also conjecture self-servingly regarding confounding and bias. They dismiss dietary confounding by citing older epidemiology studies and found no change in risk."

We acknowledge the receipt of this submission of the Law and Hackshaw paper from RJR and note that its findings are broadly consistent with the US EPA meta-analysis. Law and Hackshaw estimated a combined relative risk of 1.24 in their analysis of 34 studies and reported a p value of <0.001 for the finding. The researchers present various lines of evidence indicating that environmental tobacco smoke causes lung cancer, and conclude that "The evidence confirms beyond reasonable doubt that a causal relationship exists between environmental tobacco smoke and lung cancer."

The sponsorship of the work by these researchers was not noted in their publication.

Publication	Issue raised by RJR
6. Delamothe (1996). Whose data are they anyway? <i>British Medical Journal</i> 312:1261-1262.	"RJR submits this article to Cal/EPA as further evidence that Cal/EPA should obtain and make available to all interested parties the raw data from the study by Fontham et al...The requests for Fontham raw data are consistent with established scientific principles. Epidemiological societies encourage sharing data so that research findings are replicated..."

Cal/EPA acknowledges the receipt of this comment, and the editorial submitted by RJR regarding the sharing of raw data from research on patients.

Publication	Issue raised by RJR
7. Moolgavkar and Luebeck (1996). A critical Review of the evidence on particulate air pollution and mortality <i>Epidemiology</i> 7:420-428.	RJR notes the relevance of the Moolgavkar and Luebeck findings for air pollution, who note <ul style="list-style-type: none"> a. “the main problem faced by the meta-analyst can be summed up in one word: heterogeneity” b. “confounding is by far the most important issue in epidemiological studies, such as those of air pollution in which relative risks are small.”

Moolgavkar and Luebeck review the epidemiological studies of particulate air pollution and mortality in US cities and note that many of the studies are deficient in their control of confounding effects of other pollutants. The researchers note that most of the epidemiologic studies have been ecologic. In this sense the context of the Moolgavkar and Luebeck remarks differs from that of ETS - lung cancer analyses of analytic studies. Nonetheless problem of heterogeneity in meta-analyses is acknowledged by OEHHHA. US EPA dealt with this issue by taking a tiered approach to the meta-analysis of the ETS/lung cancer data, and by analyzing the US data separately from the data from other countries. The results of that meta-analysis are quantitatively consistent with the results found in the more recent large studies which carefully addressed issues of confounding.

OEHHHA agrees with Moolgavkar and Luebeck that confounding is an important issue in evaluating small risks, which is why the findings of well conducted studies which attempt to address the significant confounders are given more weight than poorer quality studies in judging the overall evidence for effect.

The research of Moolgavkar and Luebeck was sponsored by the American Iron and Steel Institute.

Publication	Issue raised by RJR
8. Wynder (1996) Response to Science article, <i>Epidemiology</i> faces its limits <i>Am J Epi</i> 8:747-749; Gori (1996). <i>Epidemiology, risk assessment and public policy Risk Analysis</i> 16:291-293.	RJR notes that Gori addresses the uncertainty inherent in weak statistical associations by quoting “[l]oose judgmental criteria have been introduced to give causal appearance to statistical associations: strength, consistency, specificity, temporality, response gradient, plausibility, coherence, and analogy. Such criteria are inadequate for an analytical evaluation of how uncertain causal inferences might be, and they fail to address the structural uncertainties derived from biases and confounders.” RJR also quotes from Wynder “[t]rue associations of this order [less than 2.0] are more likely to be affected by classification biases, confounding, case or control selection, and selective subgroup analysis than would be the case for large order associations.” RJR goes on to note that “Because it is uncontroverted in the record that all of the studies on ETS, lung cancer and heart disease produce, at most, ‘weak associations’, Cal/EPA must carefully apply the principles discussed by Gori and Wynder in interpreting these issues.”

Dr. Gori essentially disagrees with criteria of causality of Hill (1965; *Proc R Soc Med* 57:1073-83) used as the basis of judging effects by a variety of regulatory and authoritative bodies such as the US EPA, US Surgeon General and others. Dr. Gori has reiterated this position verbally during the April, 1997, public forum on the document, in his written comments submitted during the current public review, and on several previous occasions in verbal and written submissions. It seems to be Dr. Gori's position that none of the effects associated with exposure to ETS can be addressed epidemiologically since in his opinion the tool is too blunt an instrument to use for this purpose. OEHHA and a large number of epidemiological researchers find otherwise, but we nonetheless respectfully acknowledge Dr. Gori for his opinion.

Dr. Wynder in his commentary has greater confidence that epidemiological research can establish small effects, but he notes that to establish them "epidemiology has to do its best work.... It operates best when conducted by experienced investigators with sound medical and biologic training and insight; and it concludes optimally when all aspects of epidemiology including ecologic distribution, presence of dose response, time trends, consistency, and biologic plausibility are fully considered." Taken together, the reports of the US EPA, National Research Council, and Office of the Surgeon General, included with the recent well done epidemiological studies, have so concluded.

Publication	Issue raised by RJR
9. Biggerstaff (1995). <i>Random Effects Methods in Meta-Analysis with Application in Epidemiology</i> . Ph.D. dissertation, Department of Statistics, Colorado State University, Fort Collins	RJR in commenting on this dissertation states that "According to Biggerstaff, sensitivity analysis mandates that the authors of a study check the accuracy of all of their assumptions." RJR states that "Biggerstaff explains that the classical 'logit' analysis, the type of analysis used in the epidemiology studies relied on by both US EPA and Cal/EPA, under-estimates the confidence interval (CI) width by 5-10% compared to a Fisher exact CI". RJR states that "This issue was not considered further in Biggerstaff's analyses nor was it considered in the Cal/EPA analyses. Thus, Cal/EPA's reliance on logit analyses increases the likelihood that the agency's assumptions regarding ETS and lung cancer are not as stable as they appear to be." In discussing the results of Biggerstaff's application of the methodology to ETS RJR states that "Biggerstaff's analysis should be accorded no weight by Cal/EPA" because it does not account for publication bias, possible effects of other biases such as misclassification of smoking status, or confounding.

Biggerstaff investigated statistical methodology used in meta-analysis, focusing on the random effects model. He shows how both Bayesian and frequentist approaches may be viewed within the same hierarchical structure, thus allowing for comparisons. Methods are developed for measuring heterogeneity of study results and then accounting for it in making inferences. Biggerstaff develops a method of moments based approach to interval estimation of the heterogeneity parameter τ^2 (based on Cochran's homogeneity statistic Q), and computes two likelihood-based estimates of τ^2 for comparison in applications provided. Biggerstaff introduces sensitivity analysis based on these interval estimates as an improvement to current methodology.

The dissertation is a well written, carefully considered work, and would warrant consideration in future meta-analyses of ETS exposure and lung cancer.

Regarding the issue of confidence limits raised above, the larger differences between the values for the logit and for the exact occur for the smaller studies, as noted by Biggerstaff. For the large Fontham *et al.* study, the logit interval presented is actually smaller than the exact interval. For the strongest studies, the differences in the intervals calculated under the different methods are minor. Thus, we do not agree with the commentator that “reliance on logit analyses increases the likelihood that the agency’s assumptions regarding ETS and lung cancer are not as stable as they appear to be.”

Biggerstaff provided an analyses of the ETS lung cancer data as an example of his proposed procedure. Using crude data, unadjusted for confounders, the results of his analysis are generally supportive of the US EPA results; findings for females are highly significant with the Fisher’s method of combining p-values. The sensitivity analysis performed on the ETS studies of spousal exposure for females indicated the standard random effects analysis “is robust to estimation of the heterogeneity parameter”. It is doubtful that a significantly different findings would result from relying on the adjusted, rather than the crude data set. Also of interest is the analysis of study quality. Biggerstaff finds increasing homogeneity in the female studies with increasing measures of quality (indicated by the US EPA tiers). Yet, as noted by RJR, the application is provided as an example only.

The Ph.D. research of Dr. Biggerstaff was supported by a research assistantship provided by Dr. Tweedie.

Publication	Issue raised by RJR
10. Lee and Forey (1996). Misclassification of smoking habits as a source of bias in the study of Environmental Tobacco Smoke and Lung Cancer. <i>Statistics in Medicine</i> 15:581-605.	RJR emphasizes the following points in submitting this paper: a. When the magnitude of an association is weak, addressing misclassification bias is critical b. Misclassification biases may lead to an apparent relationship when no true relationship exists c. The US EPA report underestimates the impact of bias due to smoking status misclassification d. The Wells model that is the basis of the US EPA’s misclassification adjustment is unreliable e. The misclassification rates used by US EPA are too low.

Misclassification bias is an important consideration in interpreting epidemiological findings, particularly for small increases in risks. Lee has authored other review papers on exposure to environmental tobacco smoke and lung cancer, in which he reports that the association between ETS and lung cancer can be explained by misclassification of smokers as nonsmokers. The paper by Lee and Foley calculates bias corrections using formulae developed in the paper for additive and multiplicative models for impacts of misclassification bias. Under the same assumptions regarding the distribution of controls and cases by smoking status, and 4 classifications of smoking status (never, former, occasional, regular) as that indicated in the study by Correa *et al.*, Lee and Forey calculate a bias of 1.209 under the multiplicative model and 1.087 under the additive model. The

US EPA bias estimate was 1.10. Lee and Forey then propose a simplified model since the former requires the assumption of 6 misclassification probabilities. This model gave bias estimates of 1.185 under the multiplicative model and 1.0806 under the additive model, to be compared with estimates given just above. They then applied their method to the studies used in the US EPA meta-analysis. They performed an analysis on the 11 studies used by US EPA, concluding: “Thus our estimate [of relative risk] for the same 11 studies EPA used is 1.2 (95% CI 1.05-1.38).” They calculated this under a simpler model assuming only misclassification of ever smokers to nonsmokers and a misclassification rate of 1.75% and 3 for the concordance ratio k (*i.e.*, for m_2 the fraction of smokers whose spouses smoke and m_1 the fraction of non-smokers whose spouses smoke, $k = [m_2/(1-m_2)]/[m_1/(1-m_1)]$). Lee and Forey performed a meta-analysis on 13 studies of nonsmoking wives exposed to husband’s smoke and found that the relative risk was not statistically significant, giving 3 reasons: i) they included three studies not included by US EPA - an unpublished study by Kabat presented at the 1990 Toxicology Forum (RR=0.90, 95% CI 0.46-1.76) which has been superseded by Kabat, 1995; Brownson *et al.*, 1992; and Stockwell *et al.*, 1992; ii) the individual study data they used give slightly lower relative risks; iii) the bias calculated by US EPA is substantially lower than the bias they estimate (1.03 versus 1.08). They indicate in this regard “the most notable difference is for the largest study [Fontham *et al.* [US EPA used the 1991 publication, Lee and Forey, the 1994 report] where we estimate 1.08 and the EPA only 1.01.”

With respect to misclassification in the Fontham study, Lee and Forey discuss the limitations of urinary cotinine measurements, stating that sampling of the cases occurred in the hospital. Lee and Forey fail to give credit for the effort made by authors of this study to mitigate against misclassification of smokers as nonsmokers. Samples were taken at the time of interview (Fontham *et al.*, 1991; *Cancer Epid Biomarkers Prev* 1:35-43), which did not occur in the hospital. In addition, information was obtained on each study subject’s personal use of tobacco, first from the medical record of the cancer cases, then from the patient’s personal physician. For those patients whose medical records and physicians did not indicate a history of smoking, the study subject, or if deceased, next of kin, was asked about the subject’s tobacco use. Finally, at the time of interview, a urine sample was collected. Thus, there was an extensive effort to prevent misclassification in the Fontham *et al.* study.

With regard to the general issue of misclassification of smokers as nonsmokers, there are a number of papers on the subject, in addition to those by Lee. Most recently, in a study of misclassification of smoking status among women, Riboli *et al.* (1995; *Eur Respiratory J* 8:285-290) found 1.5% of alleged nonsmokers to be light smokers; this suggests that if relative risks for ever smokers are used to correct for misclassification, the adjustment will be too large. Nyberg *et al.* (1997; 8:304-309) similarly found in their study of misclassification for two cohorts that misclassification mainly concerns light smokers or long time exsmokers. Nyberg found among misclassified men a relative risk of 1.9 (95% CI 0.4-9.9). Overall in this study, misclassification rates were lower among females reporting never smoking than among males. The general problem of ubiquitous background exposures to environmental tobacco smoke, particularly in previous decades,

and the downward bias in relative risks for nonsmokers in these studies, and possible adjustments for it, was not addressed by Lee and Forey.

With respect to the meta-analysis of 13 spousal studies performed by Lee and Forey, we note that other meta-analyses conducted since the 1992 US EPA report have reached different conclusions. For example, a meta-analysis performed by Dr. Brown (1995), which extends his meta-analysis included in the 1992 US EPA report found a pooled estimate of risk for US studies in Tier I (“those of greatest utility for investigation of a potential association between ETS and lung cancer”) of 1.3 (95% CI 1.09, 1.54). (The studies in Tier I were released subsequent to US EPA’s review.) Dr. Brown concluded in the 1995 report that “ETS is a carcinogen”.

As a matter of background, the work of Lee and Forey was supported by the tobacco industry.

Publication	Issue raised by RJR
11. Schwartz <i>et al.</i> (1996). Familial risk of lung cancer among nonsmokers and their relatives. <i>Am J Epidemiol</i> 144:544-562.	RJR notes that Schwartz <i>et al.</i> report an association between lung cancer in nonsmokers and family history of lung cancer, and provide evidence that family history is a potential confounder for studies attempting to analyze ETS and lung cancer. RJR notes that the risk estimates provided by this study for ETS exposure at home (OR 1.1, 95% CI 0.8-1.6) and work (OR 1.5, 95% CI 1.0-2.2), while adjusted for age, sex and race, are not adjusted for other factors identified in the paper.

Schwartz *et al.* conducted a case control study of lung cancer in Detroit, and reported overall a nonsignificant increase in lung cancer in those with a family history of lung cancer (i.e., in a first degree relative) (OR=1.4, 95% CI 0.8-2.5), after adjusting for age, race, and sex; the only risk factor significantly elevated overall in the study was for ETS exposure at work (OR=1.5, 95% CI 1.0-2.2). A significant risk was reported in the 40-59-year-old age group, after adjusting for smoking, occupational and medical history of each family member (RR=6.1; 95% CI 1.1-33.4). 83% of the interviews of the 257 nonsmoking lung cancer cases and 22% of the 277 controls were conducted with proxies. Limitations noted by the study authors included reliance on proxy reports of smoking, occupation, and health histories, including histories of familial lung cancer. OEHHHA notes that familial history of lung cancer has been controlled for in the large study of Fontham *et al.* 1994. A further description of the study is provided below in the response to RJR’s comment 2 below.

As a matter of background, the work was funded by the National Cancer Institute and National Institute for Occupational Safety and Health.

2. Comment Summary: There are new ETS epidemiologic studies that Cal/EPA must evaluate as it revises the section on lung cancer. RJR proposes the following additions to Tables 7.4-7.7 in the ETS report:

Table of Additions to ETS Report Proposed by RJ Reynolds

Study/location	Gender	ETS Exposure	Cases/ Controls	OR (95% CI)
Choi <i>et al.</i> 1989	F	Spouse	75/164	1.63 (0.92-2.87)
Korea	M		13/96	2.73 (0.49-15.2)
Jockel 1991	F	Partner	23/45	2.27 (0.75-6.82)
Germany	M		9/70	2.68 (0.58-12.4)
Du <i>et al.</i> (1993)	F	Husband	75/254	1.09 (0.64-1.85)
China				
Liu <i>et al.</i> (1993)	F	Husband	38/69	1.66 (0.73-3.78)
China				
Layard (1994)	F	Spouse	39/1930	0.58 (0.30-1.13)
USA	M		21/998	1.47 (0.55-3.94)
Zaridze and Zemlyanaya (1994)	F	Husband	162/285	1.66 (1.12-2.46) *
Russia		Family Member		1.08 (0.67-1.74)*
		Workplace		1.23 (0.74-2.06)*
		Childhood		0.98 (0.66-1.45)*
Cardenas (1997)	F	Spouse	150 of	1.2 (0.8-1.8)*
USA	M	Workplace	192,234	1.1 (0.6-1.8)*
Cardenas (1995)			97 of 96,532	dose-level only
			?	

Table of Additions to ETS Report Proposed by RJ Reynolds (Continued)

Study/location	Gender	ETS Exposure	Cases/ Controls	OR (95% CI)
Wang <i>et al.</i> (1995)	F	Husband	135/135	1.11 (0.67-1.84)
China		Workplace		0.89 (0.46-1.73)
		Childhood		0.91 (0.56-1.48)
Schwartz <i>et al.</i> (1996)	F&M	Home	257/277	1.1 (0.6-1.6)*
Detroit		Workplace		1.5 (1.0-2.2)*
Shen <i>et al.</i> (1996)	F	?	70/?	0.85 (0.26-2.74)
China				
Sun <i>et al.</i> (1996)	F	Husband	230/230	1.16 (0.80-1.69)*
China				
Wang <i>et al.</i> (1996)	F	?	??/?	2.5 (1.3-5.1)
China				
Ko <i>et al.</i> (1997)	F	Spouse	105/105	1.3 (0.7-2.5)*
China		Cohabitant		1.0 (0.4-2.3)*
		Workplace		1.1 (0.4-3.0)*
		Childhood		0.8 (0.4-1.6)*

Response: Of the 13 studies that RJR proposes to be included in the Cal/EPA ETS report, 4 have been reported in peer reviewed journal publications, 6 are reported in meeting proceedings, 1 is an unpublished report, and 2 are reported in foreign language journals with limited information available on study methodology:

Study	Type of study report
Choi <i>et al.</i> (1989)	Foreign language article (Korean). Information on study methodology very limited.
Jockel (1991)	Meeting proceedings paper
Du <i>et al.</i> (1993)	Meeting proceedings paper
Liu <i>et al.</i> (1993)	Peer reviewed journal article
Layard (1994)	Unpublished manuscript
Zaridze and Zemlyanaya (1994)	Foreign language article
Cardenas <i>et al.</i> (1997); Cardenas (1995)	Peer reviewed journal publication; Ph.D. thesis
Wang <i>et al.</i> (1995)	Meeting proceedings paper. Should be

| Wang *et al.* 1996

Study	Type of study report
Schwartz <i>et al.</i> (1996)	Peer reviewed journal publication
Shen <i>et al.</i> (1996)	Meeting proceedings paper.
Sun <i>et al.</i> (1996) China	Meeting proceedings abstract
Wang <i>et al.</i> (1996)	Meeting proceedings paper.
Ko <i>et al.</i> (1997)	Peer reviewed journal publication

As outlined below, none of the reports cited contradict the overall findings of Cal/EPA, although some of the studies from China suggest that the relative risks from ETS exposure may be greater in China than in Western countries. Without a more extensive discussion of study methodology than is provided in the meeting proceedings for many of these studies, definitive conclusions in this regard cannot be made. The studies which were published in peer-reviewed literature (Liu *et al.*, 1993; Schwartz *et al.*, 1996; Cardenas *et al.*, 1997; Ko *et al.*, 1997) have been added to the chapter on carcinogenic effects. The others are summarized below.

Choi *et al.* (1989; *Korean Journal of Epidemiology* 11:66-80) was a hospital case-control study conducted in one hospital in Korea. Primary lung cancers confirmed by cytological histological confirmation diagnosed over a 3-year period were eligible. Two hospital controls were interviewed per case. Controls were individually matched to cases on age, gender, date of hospital admission and area. Patients admitted for tobacco-related diseases were excluded as controls but the actual diagnoses of controls were not presented. Questions were asked regarding the smoking status of the spouse and duration of exposure to spouse's smoke but few additional details are provided on ascertainment of exposure to ETS. Results on ETS were based on 13 male cases and 96 control males who never smoked and 75 female cases and 164 female controls who never smoked. In males, based on very small numbers (2 cases and 6 controls) who were exposed to spouses who smoked, there was a 2-fold increased risk (RR=2.73, 95% CI 0.49-15.21). In females, the RR was 1.6. In further analysis by number of years nonsmoking women were exposed to spouses' smoking, RJR calculated that there was a trend of increasing risks with increasing years (1-20, 21-40, 41+) of exposure (p for trend = 0.06). These were crude ORs which were calculated based on the numbers presented. The findings of this small study are not inconsistent with those reported in the Cal/EPA document, but the limited discussion on study design make overall interpretation of this study difficult.

Jöckel (1991; VDI Reports 888, Association of German Engineers, Mannheim Colloquium 23-25, April 1991), a proceedings paper, reports a meta-analysis on 14 studies of ETS and lung cancer (RR=1.35, 95% CI 1.2-1.52) and provides "initial results of an ongoing study on the relationship between lung cancer and passive smoking." The ongoing study is a case control study of the relationship between lung cancer and risks at the workplace, based on 1000 cases and 1000 controls from the Bremen and Frankfurt regions of Germany. 33 cases and 115 controls who regarded themselves as complete nonsmokers and occasional smokers served as the basis of the report. Details on study design are not provided, and the author notes that the results should not be viewed as conclusive but rather as a first interim report on the study. Jöckel reported a non-

significantly elevated RR associated with passive smoking (2.46, 95% CI 0.94-6.43). Under an analysis using an alternative exposure index which also includes sources of ETS exposure besides that associated with spouse's smoking, a significantly elevated RR was reported (2.64, 95% CI 1.15 -6.07). Further, for exposures characterized as high relative exposures, relative risk was also reported to be significant (RR=3.43, p=0.018). Because the reporting of study design is absent, and the report is an interim one, we would be reluctant to include it in the Cal/EPA report. Nonetheless, we note that the results are not inconsistent with those provided in the report.

Du *et al.* (1993; *Proceedings of Indoor Air '93*, Volume 1, pp 511-516) report results of a case control study on "never smoking females" in Guangzhou, China. Few details are provided on study methodology, other than to note that from "1980 to 1988 every case of lung cancer death was further analyzed using a standardized questionnaire containing 31 questions. Information was obtained retrospectively from relatives and verified." There is no discussion of the completeness of the information obtained from relatives and hospital records, the total number of lung cancer deaths identified during the study period, or the definition used to determine being exposed to ETS exposure or not exposed to ETS. There were also two other studies; one included lung cancer deaths in 1985 and a second study included lung cancer deaths in 1986. The relationship of these two substudies to the overall study of lung cancer deaths identified in 1980-1988 is unclear. Study methods of the substudies were also poorly described. The ETS exposure history of women who died from lung cancer were compared to two different control groups, those who died of non-malignant conditions and those who died of non-lung malignant conditions. In the former analysis, compared to women who were married to nonsmokers, those married to smokers showed a nonsignificant increased risk of lung cancer (OR=1.19, 95% CI=0.66, 2.16). In the latter analysis, lung cancer cases did not differ from control women in husband's smoking history (OR=1.00). Risk of lung cancer was not significantly associated with number of cigarettes smoked or years of husband's smoking in both comparisons. The ORs presented appear to be unadjusted ORs. The severe methodologic shortcomings of the study limit the usefulness of this study in evaluating the effects of ETS exposure.

RJR submitted an unpublished and undated paper by Maxwell W. Layard of Layard Associates, Alameda, CA, entitled "Ischemic heart disease, lung cancer, and spousal smoking in the National Mortality Followback Survey." A detailed description and critique of the study methods can be found in the section on case control studies of cardiovascular effects (section 8.1.2) of the OEHHA ETS report. The analysis on ETS exposure and lung cancer utilized the same control group as the analysis on ETS exposure and coronary heart disease. Next of kin of decedents were asked questions on a number of factors. The decedents included in Layard's study were restricted to those reported by next of kin to be lifetime never-smokers, defined to be those who had never smoked 100 or more cigarettes in their entire lives. Decedents were excluded if they had never had a spouse, or if information on spousal smoking was unavailable. After applying these exclusions, Layard found 21 male and 39 female lung cancer deaths. The control group consisted of 998 male and 1930 female decedents. As noted by Layard, male lung cancer

cases were significantly older than male controls while female lung cancer cases were nonsignificantly older than female controls in this analysis. There was also a significantly higher percent of black males in the lung cancer case group than in the male control group. After adjustment for age, Layard reported a nonsignificant elevated OR for males (1.47, 95% CI 0.55-3.94), and a non-significant decreased OR for females (0.58, 0.30-1.13) of smoking spouses. The method of age adjustment was not described. Layard notes that “[t]here were too few lung cancer cases among never-smokers in the NMFS to provide much information about ETS exposure and lung cancer.” We agree and emphasize other limitations of this study which include lack of sufficient detail on exclusions and the method for age adjustment and the significantly older cases compared to controls.

Zaridze and Zemlyanaya (1994; *Experimental Oncology* [Russian] 16:441-445). RJR provided a Russian paper with an English abstract of a case control study of lung cancer risk in nonsmoking women in Moscow. The study authors report an increased risk of lung cancer in women whose husbands smoked, with an RR of 1.9 (95% CI 1.3-2.9). RJR provides in their tabulated proposed additions to the report their own ORs and confidence intervals for this and other exposure categories. Cal/EPA did not have available a full translation of the Russian article, but note that the risk reported is somewhat higher than that seen for several of the US studies. It is unclear whether this is due to study design, or differences in ventilation or other factors.

RJR provided a proceedings paper presented at the International Symposium on Lifestyle Factors and Human Lung Cancer held in Guangzho, China December 12-16, 1994, by Wang *et al.*, reporting on a case control study conducted in Shenyang, China between April 1992 and May 1994 (Lung Cancer 14, Suppl 1, pp S99-S105). RJR submitted the proceedings paper in its comments to Cal/EPA as Wang *et al.* 1995 (to clarify, the proceedings paper was published in 1996 rather than 1995). This was a hospital-based study conducted in Shenyang which included all lung cancers identified (n=135) in nonsmoking women during a two-year period. Approximately half the lung cancer cases were histologically confirmed. An equal number of age-matched controls were identified from the general population of urban Shenyang. An in-person interview was conducted with controls and cases while they were still in the hospital. Exposure to ETS at home before and after marriage and at the workplace was asked although the level of detail obtained was not described. For example, it cannot be determined whether lifetime exposure to ETS at the workplace was obtained. Lung cancer in nonsmoking women was not associated with ETS exposure in the workplace (OR 0.89, 95% CI 0.45-1.77), before marriage (0.91, 95% CI 0.55-1.49), or from spouse’s smoking (OR 1.11, 95% CI 0.65-1.88). Elevated ORs were observed in the higher exposure groups for numbers of cigarettes smoked by spouse per day or the number of years lived with a smoking spouse, but the results were not statistically significant. This is a small study, and the magnitude of the result for women with spouses who smoke is not inconsistent with that reported in the Cal/EPA document. It is not clear what adjustments for confounders were made to produce the results presented.

At the International Symposium on Lifestyle Factors and Human Lung Cancer held in Guangzhou China December 12-16, 1994, Shen *et al.* (1996; Lung Cancer 14, Suppl 1, pp S107-S112) reported on a case control study for primary lung cancers. This was a hospital-based study conducted in Nanjing, China. Primary lung cancers diagnosed from one hospital between 1986 to 1993 were included in this study. There were a total of 83 squamous cell carcinomas and 180 adenocarcinomas of the lung. Healthy controls were identified from the general population of Nanjing. The study methods of this study were poorly described. The representativeness or completeness of the cases identified for this analysis cannot be determined. Relevant information such as age, gender and active smoking distribution of the case and control groups was not presented. These investigators reported that in a multivariate analysis exposure to ETS was not a significant risk factor at the $p \leq 0.05$ level for either squamous cell carcinoma or adenocarcinoma. In addition, they reported that “In a separate case control study involving 70 nonsmoking females with adenocarcinoma, exposure to environmental tobacco smoke (ETS) of > 20 cigarettes/day had a relative risk of 0.85; 95% CI, 0.26-2.74 (data not shown).” No other details on this study were provided in the report. Because of limited information on study design and reporting, interpretation of this and the multivariate analysis study described above is difficult. One should not try to interpret results of such poorly described (and conducted) studies.

At the International Symposium on Lifestyle Factors and Human Lung Cancer held in Guangzhou China December 12-16, 1994, Wang *et al.* (1996; Lung Cancer, 14 Suppl 1, S99-S105) presented a hospital-based case-control study of risk factors for lung cancer, conducted in Guangzhou, China between 1990 and 1993. Lung cancer-cases and hospital controls were identified from 5 hospitals in the study area. There were 291 male and 99 female lung cancer cases of whom 10% and 83% of subjects were nonsmokers, respectively. Controls were patients who were hospitalized during the same time period as the cases but did not have lung diseases. The percent of male and female controls who were nonsmokers was not specified. The OR for lung cancer was 1.79 (95% CI=1.08-2.97) associated with ETS exposure at home and 1.68 (95% CI=1.13-2.48) associated with ETS exposure at work. These risk estimates were presumably obtained in a multivariate logistic regression model and were calculated for smokers and nonsmokers combined, adjusting for active smoking. The authors described that among nonsmokers, the OR associated with ETS exposure was 2.5 (95% CI=1.3, 5.1). Since little information was provided to determine how this risk estimate was derived, these results are difficult to interpret.

RJR submitted an abstract of a symposium paper by Sun *et al.* (Lung Cancer, 14 Suppl 1, S249). The abstract describes a population based case control study conducted in Harbin, China “which attempts to clarify the relationship between exposure to ETS and the risk for lung cancer in ‘never smoking’ women.” 230 non-smoking women with histologically confirmed primary lung cancer and 230 nonsmoking controls were interviewed in person. ORs were derived for exposure to ETS during childhood, adolescence and in adulthood at home and in the workplace using logistic regression analyses, adjusting for age and education. Statistically significant results were reported

for exposures to ETS in both home and workplace (OR=2.92; 95% CI 1.89-4.49), during childhood (OR=2.29, 95% CI 1.56-3.37), adolescence (OR=2.60; 95% CI 1.77-3.83), and adulthood (OR=1.83; 95% CI 1.20-2.80). Maternal (OR=2.05; 95% CI 1.29-3.27) and paternal (OR=2.35; 95% CI 1.56-3.54) smoking conferred an increased risk of lung cancer, but no significant association was reported for spousal smoking (OR=1.16; 95% CI 0.8-1.69); in fact, an OR of 0.86 (95% CI 0.45-1.65) was reported for women who lived with husbands who smoked for more than 35 years. Still, “the number of reported years of exposure to ETS and the amount of lifetime exposure to ETS in the home were significantly associated with lung cancer risk.” Interpretation of this study is difficult given that detailed information on study methodology has not been reviewed. Nonetheless we note strengths of the study appear to include in-person interview of study subjects, and histological confirmation of lung cancer. Although suggestive elevated risks were reported associated with various measures of ETS exposure, results from this study can be evaluated only when they are presented in a full-length report.

3. Comment Summary: Draft tables contain numerous errors and provide statistical results that must be corrected or explained:

Comments by RJ Reynolds on Tables 7.4-7.7	OEHHA Response
RJR Comments on Table 7.4	
Does not include Layard (1995), Cardenas <i>et al.</i> (1997), Schwartz <i>et al.</i> (1996)	The Cardenas <i>et al.</i> and the Schwartz <i>et al.</i> studies have been added to the document. OEHHHA notes that inclusion of these studies does not change the conclusions of the report. The Layard paper is unpublished, not peer reviewed, and methodological details are lacking.
Entry under “ethnicity” and “matching variables of lifetime nonsmoking controls” for Fontham (1994) is not appropriate. Publications indicate matching on race only.	The table has been clarified to indicate that cases and controls were matched on the basis of age, area, and race.
Table reports 100% of cases in Fontham confirmed by independent histologic review; publication reports 85%	100% of the cases in the Fontham <i>et al.</i> study were histologically confirmed. The 85% represented an independent (i.e., a second) review of the already histologically confirmed diagnosis. The main purpose of the second review is to determine the concordance on histologic classification between community pathologist versus one pathologist.
Biologic markers entry for Fontham fails to indicate that only 53.3% of cases and 83.3% of controls were tested for urinary cotinine and problems with using cotinine for this purpose (short half-life, “smokers with lung cancer are likely to quit smoking as symptoms become apparent”). Use of cotinine preferentially excludes smokers from controls but not cases.	The table now indicates that cotinine measurements were taken on 81% of the self-respondent cases and 83% of the controls. The finding of increase in lung cancer among self-respondents was significant for all lung cancers (p=0.0006) and for adenocarcinoma (p=0.0005).
Table fails to indicate that analyses are available by Butler for the 1992 Brownson study. Use of Butler’s analyses shows effect of using self versus proxy respondents	The Butler analysis is discussed in responses to comments below and above.
RJR Comments on Table 7.5	
Table does not include Layard (1995), Cardenas <i>et al.</i> (1997), Schwartz <i>et al.</i> (1996)	The Cardenas <i>et al.</i> study has been added (Table 7.5A); the Schwartz <i>et al.</i> study is described in the text. OEHHHA notes that inclusion of these studies does not change the conclusions of the report. OEHHHA notes that the Layard paper is unpublished, not peer reviewed, and methodological details are lacking.
Reported results for Fontham have not been analyzed correctly for the reported interaction of childhood and adulthood exposure (references Butler’s comments to OSHA)	The Butler analysis is discussed in responses to comments below and above.
RJR Comments on Table 7.6	

Table does not include Zaridze & Zemlyanaya (1994), Wang <i>et al.</i> (1995), Sun <i>et al.</i> (1996), Ko <i>et al.</i> (1997)	OEHHA notes that inclusion of these studies, which are described above, would not change the conclusions of the report.
Table indicates number of cases among unexposed in Janerich <i>et al.</i> is 37 but paper lists 57. Crude OR and CI for exposed versus unexposed can be computed as 1.3 (95% CI 0.85-2.00)	The number of cases in the table has been corrected. The information in the table allows the reader to combine cases and controls in the different dose groups and calculate confidence intervals should they wish to do so for additional groupings.
Fontham <i>et al.</i> should not be used until interaction issue identified by Butler is resolved. Table lists unexposed controls for father smoker in childhood as 699 but the paper lists this count as 669. The table lists the OR for 18+ years of childhood exposure as 0.89 but the paper lists this as 0.88.	The table has been corrected. The issue regarding Butler's analysis is addressed in responses to comments below.
RJR Comments on Table 7.6 (continued)	
The OR and CI listed in the table were not provided in the paper by Kabat and Wynder	A notation has been added to the report that these were calculated from the data provided in the paper.
Kabat <i>et al.</i> 1990 should be Kabat 1990. The results were superseded by Kabat <i>et al.</i> 1995. This entry should be deleted	Kabat 1990 has been removed from the table.
For Wu-Williams <i>et al.</i> , the table lists the unexposed case count for father smoked as 335 but the paper lists it as 235. The CIs listed in the Table were not in the paper.	The table has been corrected and a notation added.
Persahagen <i>et al.</i> is listed in the table as a 1986 paper but it is a 1987 paper. The exposure surrogate should be at least 1 parent smoked rather than "parents smoked". Case counts for exposed and unexposed are reversed. Table lists counts for controls of 76 exposed and 18 unexposed which are not consistent with the published CI but are consistent with the OR.	Study date has been added. The table entry with respect to parental smoking has been made clearer. We note that the numbers now shown in the Table 7.6 of the OEHHA report were presented in Table 5 of Pershagen <i>et al.</i> (1987). Although the number and % of cases and controls with at least one parent smoker are shown in Table 2 of Pershagen <i>et al.</i> , we cannot reproduce the odds ratio of 1.0 shown in their Table 5, if we infer the number of controls based on parents' smoking habits.
Comments by RJ Reynolds on Tables 7.4-7.7	OEHHA Response
RJR Comments on Table 7.7	
Table does not include Zaridze & Zemlyanaya (1994), Wang <i>et al.</i> (1995), Sun <i>et al.</i> (1996), Ko <i>et al.</i> (1997)	Inclusion of these studies, which are described above, would not change the conclusions of the report. Wang <i>et al.</i> (1995) is a proceedings paper; Sun <i>et al.</i> is an abstract. Zaridze and Zemlyanaya (1994) published in a Russian journal provides few methodological details.
Kabat and Wynder upper CI is 10.6 not 10.4	We have rechecked our calculations and still get 10.4 for the upper CI.
Janerich <i>et al.</i> reported as "no association" in Table but OR and CI are available in the paper as 0.91 (95% CI: 0.80-1.04)	The numbers have been added to the table.
Brownson reported as no overall association but Butler (1995 comments to OSHA) gives OR and CI	This is reported in the table as no association overall, but OR and CI are given in the table for highest exposure quartile.
Fontham <i>et al.</i> should not be used until the interaction issue identified by Butler is resolved	Butler's analysis of the Fontham paper is discussed in responses to comments above and below.
Kalandidi <i>et al.</i> OR and CI are inappropriate crude estimates comparing risk for housewives (as unexposed controls) versus ETS exposure. This comparison is invalid. The paper provides an estimate of 1.08 (95% CI 0.24-4.87) for a comparison of extreme quartiles of ETS workplace exposure.	We note that while 1.08 (95% CI 0.24, 4.87) was presented on page 19 of this report, it is unclear how this was obtained. The number we presented in our Table 7.7 is based on the numbers presented in Table 2 of Kalandidi <i>et al.</i> We calculated a crude odds ratio. We used 'some' and 'minimal' as exposed, and housewife as 'not exposed'. If we used 'housewife and minimal' as not exposed, the crude odds ratio becomes larger - 1.85 (95% CI 0.78, 4.39).
Koo <i>et al.</i> listed in table as 1987 but it should be 1984. 1987 paper updates spousal exposure results only. 1994 paper provides counts which are not listed in the table. Counts yield a 95% CI of 0.15-5.37.	Confidence limits added to the table and date of the report changed.
Table does not provide CI for Shimizu <i>et al.</i> , but paper does (0.69-2.01)	We were unable to find this confidence interval in the paper by Shimizu <i>et al.</i> The raw data for the calculation of the confidence intervals is not presented either.
Wu-Williams <i>et al.</i> exposed case count and OR is incorrect.	The table has been corrected to indicate that the case count is 228. The odds ratio of 1.2 (0.93, 1.57) is adjusted for center, age and education. The odds ratio of 1.06 (0.8, 1.4) is adjusted for, in addition to center, age, education, heating practices,

4. Comment Summary: “The US EPA (1992) report is a defective benchmark for Cal/EPA’s analysis of ETS and Lung Cancer.” RJR reiterated several of its previously submitted comments critical of the US EPA 1992: “US EPA ignored problems inherent in interpreting the weak and inconsistent associations reported in the ETS and lung cancer studies;” “U.S. EPA incorrectly analyzed confounding in the epidemiologic studies by employing an improper definition of confounding, ignoring most of the relevant data, failing to assess joint confounding, and failing to quantify the amount of bias introduced by confounding;” “U.S. EPA underestimated the influence and uncertainty of smoking status misclassification bias on the epidemiologic studies by employing a model that ignores statistical variability in the input parameters and by basing its analyses on the limited and biased subset of the then-available data;” “U.S. EPA’s analysis is affected by publication bias;” “U.S. EPA’s analyses do not rule out chance as an explanation for the statistical association reported;” “U.S. EPA employed less rigorous statistical trend-test analyses to evaluate dose-response because the traditional, and more rigorous, tests employed by statisticians provide results inconsistent with U.S. EPA’s conclusions;” “U.S. EPA’s use of meta-analysis to summarize the ETS epidemiologic studies was improper.”

Response: The US EPA report is the most recent of three authoritative reviews on lung cancer and exposure to environmental tobacco smoke, the other two being the 1986 Report of the Surgeon General and 1986 National Research Council document *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*. The three reviews found lung cancer to be causally associated with ETS exposure. They, and OEHHA in its review of the four recent studies considered the evidence in light of the magnitude of the relative risk associated with exposure to ETS. The study of Fontham *et al.* which went to great lengths to address confounding and misclassification bias, and their findings are consistent with the magnitude of the risk indicated by the US EPA. The recently released prospective study of Cardenas, which has been added to the final document, is consistent with the magnitude of the risk reported by the US EPA. The US EPA assessment was complete, and addressed the extensive data available on ETS up through 1991. Where possible, rates adjusting for confounding were used, and adjustments for joint confounding were made. The issue regarding publication bias is discussed at greater length above in response to comments by Dr. Tweedie and others. As the US EPA and other analyses show, it is very unlikely that the observations from epidemiological studies are due to chance alone. Regarding trend tests, the ones relied on by US EPA are the same ones typically used to evaluate dose related trends of epidemiological studies. These tests are widely used by epidemiologists and biostatisticians in reporting study results in peer-reviewed journals. The US EPA meta-analyses were subjected to considerable peer-review, including review by the US EPA Science Advisory Board, which endorsed the Agency’s use of meta-analysis. US EPA’s meta-analysis explicitly addressed the issue of heterogeneity. While there is always room for improvement with methodological developments and additional data, the result of the

1992 meta-analysis appears robust, as indicated by the comparable findings subsequently reported in the prospective study of Cardenas *et al.* (1997) and Fontham *et al.* (1994).

5. Comment Summary: RJR reiterated its contention that epidemiological research since 1992 contradict US EPA conclusions, and in doing so discussed its interpretation of studies by Stockwell *et al.*, 1992, Brownson *et al.*, 1992, Fontham *et al.*, 1994 and Kabat *et al.*, 1995.

Response: Comment acknowledged.

William Butler of Environmental Risk Analysis, for RJ Reynolds

1. Comment Summary: Cal/EPA's response to Dr. Butler's comments previously submitted on the lung cancer section was inadequate. In that submission the methodology used in the analysis of the Fontham *et al.* (1994) epidemiological study (*JAMA* 271:1752-1759) was criticized, and an alternative analysis by Dr. Butler presented. Dr. Butler clarified at the April 19, 1997, workshop that his analysis involved constructing a single control group from data presented in the Fontham *et al.* paper. From his reanalysis of the Fontham *et al.* data he concluded that women exposed to ETS both in childhood and as adults were not at an elevated risk of lung cancer. He maintained that women who did not have adult exposure but did have childhood exposure were at significantly lower risk, and that this was the sole source of the association observed.

Response: As we have noted in the previous response (Appendix A), the reanalysis conducted by Butler is erroneous. The intent of table 8 in the Fontham study is to investigate the effect of adult ETS exposure on risk of lung cancer conditional on childhood ETS exposure. Contrary to Butler's assertion that there is no increase in lung cancer risk associated with adult ETS exposure, there is a clear indication of increasing risk with increasing years of adult ETS exposure among women who had no childhood exposure and women who had childhood exposure in table 8. As also shown in the previous table of the Fontham study, there was little indication of an increased risk with lower levels of adult ETS exposure (the ORs for 1-11 and 12-28 years were 0.82 and 1.12., respectively). Butler's method of combining exposure categories (i.e., 1-11, 12-28, 29-47, 48+ smoker years) ignores the results demonstrating higher risk estimates associated with higher levels of exposure.

In a second table, Butler used no adult ETS exposure and no childhood ETS exposure as the baseline category. Women with no ETS exposure but childhood ETS exposure (5 cases and 44 controls) were simply dropped from the analysis. Although the baseline group was comprised of women with no childhood and no adult ETS exposure (i.e., considering both exposure variables separately), the rest of the table combined individuals irrespective of childhood ETS exposure. Selective dropping of study subjects and combining exposure groups when convenient are hardly correct methods of data analysis.

2. Comment Summary: Cal/EPA's response to Dr. Butler's previously submitted analysis of the Brownson *et al.* study was inadequate. As explained at the April 19, 1997, public forum, Dr. Butler had access to the raw data for this study. He segregated the data into two groups: those for which the interviews were conducted in person, and those for which a surrogate was used. He reported that among those with direct interviews there was no increase in risk with ETS exposure.

Response: The Butler analysis of the Brownson *et al.* study is laid out in a submission by Butler to the federal Occupational Safety and Health Administration (OSHA). He begins by presenting data from Table 2 of the Brownson *et al.* paper. He then presents his results after segregating the cases for never smoking women into two groups, those

directly interviewed and those with surrogate interviews. Odds ratios of order 1.1 are reported for the highest dose groups (pack-years \times hours/day) interviewed directly, and of order 1.5 for the highest dose groups associated with surrogate interviews. The increases are statistically significant for the surrogate interviews, for both spousal only and all household members as the source of exposure. The small increases reported in the direct interview group are not statistically significant. The confidence intervals reported by Butler for the high exposure groups subjected to direct interview are wide and overlap with the surrogate interview group (all household members, direct interview [0.7, 1.8] versus surrogate interview [1.0, 2.1]; spouses only, direct interview [0.7, 1.8] versus surrogate interview [1.0, 2.1]), reflecting the lack of significance for the differences between the direct and surrogate interview groups. When the direct interview and surrogate interview high dose surrogate groups are combined, the results are statistically significant (all household members 1.0 (95% CI 1.0, 1.8); spouses only 1.3 (1.0, 1.7)).

Brownson reported an odds ratio of 1.8 (95% CI 1.1, 2.9) for lifetime nonsmokers reporting heavy exposure to ETS. Reanalyses by Butler, if they were done, of the associated data were not submitted to OEHHA or to federal OSHA.

Comment Summaries and Responses on Chapter 7: Sections on Cancers Other Than Lung Cancer

Philip Morris

Philip Morris, USA, submitted by Richard Carchman, Scientific Affairs

Nasal sinus cancer

1. Comment Summary: The criteria for listing nasal sinus cancers as being “causally” associated with ETS exposure are not given in the document. The text does not mention a causal relationship.

Response: The wording of the text in Section 7.3.1.3 has been changed to reflect the text in the executive summary.

2. Comment Summary: References are not provided to support the assertion that active smoking is a causal factor for cancers of the sinus cavity. The 1982 and 1989 Surgeon General’s reports and the IARC Monograph (No. 38) do not mention nasal sinus cancer in their discussions of cancers purportedly associated with active smoking. However, OEHHA claims that active smoking is firmly established as a causal factor for cancers of the nasal sinus cavity.

Response: Several studies are referenced in Section 7.3.1.1 which indicate the presence of a significant association between tobacco product use and nasal sinus cancer. The increased risk is as high as 5-fold with heavy smoking. While it is true that the 1982 and 1989 Surgeon General’s report and the IARC Monograph did not mention nasal sinus cancer in their discussion of cancers, this may reflect, in part, the large number of health endpoints that have been associated with tobacco smoking and the fact that information on different health endpoints were not all available or known at the time these reports were prepared. As an example, when the 1982 Surgeon General’s report was published, relatively little was known about the risks associated with active smoking and stomach and cervical cancers, and thus the smoking effects on these two cancer sites were not discussed until the 1989 report. It is of note that the first epidemiological study which compared the active smoking history of patients with nasal cavity cancer and those of a control group was published only in 1981 (Elwood, 1981) and thus much of the information on the health effects of smoking on nasal sinus cancers became available only during the 1980s.

3. Comment Summary: The 1982 and 1989 Surgeon General’s reports and the IARC Monograph (No. 38) do not mention nasal sinus cancer in their discussions of ETS. OEHHA states that there are some data on the role of ETS for other cancer sites, including cancers of the nasal sinus cavity.

Response: The studies that contain data on the role of ETS and nasal sinus cancers all showed statistically significant positive effects and are discussed in detail in the ETS document in Section 7.3.1.2.

4. Comment Summary: There is a lack of significance in all but one of the studies mentioned by OEHHA in support of the claim that ETS is causally associated with nasal sinus cancer. The single estimate that is significant [the Fukada and Shibata study] contains an extremely wide confidence interval because it is based on only 9 cases. Table 7.8 clearly shows that only one of the reported risk estimates has a confidence interval that excludes 1.0.

Response: In fact, all three studies are statistically significant; two of the studies have group comparisons with p values less than or equal to 0.05, while the third shows a significant trend for increasing cancer risk with number of smokers in the household ($p=0.02$). In response to this comment, the statistical significance of these studies has been included in the revised document. As noted above (see response to comment 1 of Gio Gori), the Fukada and Shibata study's report of a RR of 5.73 associated with greater than one smoker in the household was based on a small number of cases ($n=9$) and controls ($n=5$). We have noted the wide confidence interval for this point estimate in the Document (pg 7-27) and have presented a more stable risk estimate associated with any smoker in the household ($RR=1.96$, 95% $CI=0.8-4.5$; pg 7-27).

5. Comment Summary: The sample sizes of the nasal sinus cancer studies total only 91 cases, which is not sufficient to support a conclusion of causality.

Response: Nasal sinus cancer is extremely rare; it accounts for 0.2 percent of all invasive incident cancers and 1.4% of respiratory cancers. Thus it is not surprising that there have been relatively few studies on nasal sinus cancer and that the sample sizes of nasal cancers among nonsmokers were limited in these studies.

6. Comment Summary: The study by Hirayama did not account for the age of the subject, but only the spouse's age, which is not a standard approach in epidemiology. Caution should be used in applying the reported results of the Japanese studies to the United States population, since paranasal sinus cancers are more common in Japan than in the United States. There may be ethnic-specific and lifestyle risk factors that have not been considered.

Response: These comments were previously raised and considered.

7. Comment Summary: OEHHA makes the statement that "The results have been observed in studies conducted in eastern and western countries, in males and females..." on p. 7-28. This statement misrepresents the available data reported for only one sex in each of two countries.

Response: In response to this comment, we have changed the wording in the document so that the subjects studied are clearly identified.

Cervical cancer

1. Comment Summary: OEHHA does not indicate how it reached a conclusion of “suggestive” evidence for causality for cervical cancer. In fact, OEHHA’s statements do not mention a causal relationship. The rationale for this designation are not presented in the Chapter 7 text.

Response: The weight of evidence evaluations are explained in Section 1.4. Regarding the designation of suggestive evidence: “Effects considered to have suggestive evidence of a causal association with ETS exposure are those for which a causal interpretation can be considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence”.

2. Comment Summary: Both OEHHA and the National Institutes of Health acknowledge that HPV infection is an etiological factor in cervical cancer. Given this acknowledgement, it is curious that OEHHA would even evaluate ETS exposure in terms of “causality”. Some have considered active smoking to be a “co-factor” for cervical cancer, it therefore seems premature to conclude that there is suggestive evidence that ETS is causally associated with this disease, as OEHHA claims.

Response: While it is clear that HPV infection can lead to cervical cancer, this fact does not preclude the presence of other causal factors in the etiology of cervical cancer. Smoking has been reported to be a risk factor for cervical cancer irrespective of HPV infection, as discussed in Section 7.3.2.1. In their analysis of potential confounders, Coker *et al.* (1992) found no difference in HPV positivity, herpes, gonorrhea, or chlamydia between active smokers and non-smokers. Despite this, the authors found a significant association between active smoking and cervical neoplasia.

3. Comment Summary: OEHHA’s review of the literature is incomplete. Two recent studies address the risk of cervical cancer from ETS exposure (Munoz *et al.*, 1996; Bosch *et al.*, 1996). These studies concluded that there was no association between ETS and cervical cancer that could not be explained by confounding variables. OEHHA did not include these articles.

Response: OEHHA thanks the commentator for the contribution to the document. The results from these 2 studies are consistent with the present designation of suggestive evidence of causality, and so do not change the document’s conclusions. A summary of the results of these two studies (Munoz *et al.*, 1996; Bosch *et al.*, 1996) has been added to the chapter on carcinogenic effects.

4. Comment Summary: OEHHA only reports 2 of the 4 available studies in Table 7.9.

Response: In response to this comment we have added the additional 2 studies to Table 7.9.

5. Comment Summary: The Slattery *et al.* study only found statistically significant effects of ETS for the highest exposure group for all reported ETS exposure or for home ETS exposure. Additionally, the Slattery *et al.* study does not even provide the numbers of cases and controls for the different levels. This incomplete reporting of the data makes interpretation of the study's results quite difficult.

Response: The numbers presented in Table 5 of Slattery *et al.* (1989) included smokers and nonsmokers. As noted in our Table 7.9, the number of nonsmoking cases and controls was not presented.

6. Comment Summary: For the above reasons, there is sufficient uncertainty to make the interpretation of the studies of ETS and cervical cancer difficult. Many of the reported risk estimates are not statistically significant. The studies have generally failed to adequately consider potential confounding factors. OEHHA's conclusion is therefore unwarranted.

Response: The two significantly positive case-control studies cited in Section 7.3.2 are suggestive of a causal association between ETS exposure and cervical cancer. Confounding variables were accounted for more completely in some studies than in others. Biomarkers of exposure to ETS indicate the presence of tobacco smoke constituents in cervical mucus of nonsmokers. The hypothesis that carcinogenic components of tobacco smoke may adversely affect the cervical epithelium is supported by the presence of DNA adduct levels in the cervical epithelium of nonsmokers.

7. Comment Summary: OEHHA now briefly mentions confounders in the context of the data collected in the epidemiologic studies cited. However, OEHHA should go much further in extending its discussion of the confounding variables, since these are the most important issue in evaluating cervical cancer studies.

Response: This issue has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

8. Comment Summary: The Hirayama *et al.* (1981) study fails to account for sexual activity or HPV infection. This study therefore provides essentially no information relevant to the question of ETS exposure and cervical cancer risk.

Similarly, Sandler *et al.* (1985) did not account for sexual activity.

Slattery *et al.* (1989) undermatched controls with regard to sexual activity, religious background, and education.

Response: The deficiencies in accounting for potential confounders mentioned by the commentator are all mentioned in the ETS document in the discussions on each study (Section 7.3.2).

9. Comment Summary: OEHHA omitted two important studies (Holly *et al.*, 1992; Cress *et al.*, 1994) that discuss the relationships between active or passive smoking and a number of potentially confounding factors.

Response: Section 7.3.2.1 describes the importance of controlling for confounding and cites recent articles. OEHHA acknowledges these papers as being of interest. Because they do not raise new issues, and the confounding factors in the cervical cancer studies are already adequately discussed in the ETS document, these two papers have not been added.

The Tobacco Institute

The Tobacco Institute, submitted by Clausen Ely of Covington and Burling

1. Comment Summary: The nasal sinus cancer studies have several serious problems:

- a) The three studies are too few and are not properly designed.
- b) There is no scientific basis for the claim that ETS presents a greater or equal risk than active smoking.
- c) Biases and confounding factors have not been addressed.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

2. Comment Summary: OEHHA's conclusion about the role of ETS in cervical cancer has assumed a categorical designation of "suggestive of a causal association", whereas the conclusion in the previous draft was more cautious. OEHHA relies on no new data for this change. It is not scientifically justified or reasonable to conclude that these weak and conflicting data are "suggestive" of a link between ETS and cervical cancer.

The DNA adducts and nicotine/cotinine found in cervical cells cannot be used by OEHHA as a link between ETS and cervical cancer since these are found in every tissue of exposed individuals, without any apparent "link" in many tissues.

Hirayama (1981) said that husband's smoking habits "have no effect on their wives' risk of developing other major cancers, such as cancer... of the cervix".

Slattery (1989) found that there is the same risk for smokers and ETS-exposed nonsmokers, which is contradicted by Crocker [sic] (1992) who found a protective effect for nonsmokers heavily exposed to ETS at home or at work.

Response: Four studies were considered in detail in the revised ETS Document. The single cohort study and one of the three case-control studies did not show statistically significant positive effects on cervical cancer, although positive trends were apparent. The remaining 2 case-control studies did show significant positive effects. Therefore, the studies are not “conflicting” as indicated in the comment. There is ample biological plausibility for the carcinogenic effects on the cervix from exposure to ETS, as discussed in Sections 7.3.2.3 and 7.3.2.4. However, chance, bias or confounding cannot be ruled out with reasonable confidence as explanations for the positive effects observed. This is consistent with the definition of suggestive evidence as given on p. 1-6 of the document.

The DNA adducts and presence of nicotine/cotinine are evidence that inhaled tobacco smoke constituents reach cervical tissue. Widespread tissue burdens of these constituents would not necessarily be expected to result in tumors in every tissue in which they occur. The same can be said for many inhaled known carcinogens. There are usually specific chemical and biological characteristics which determine a target tissue.

The results of the study by Coker *et al.* (1992) were not statistically significant and this is stated in the Document. It is incorrect to consider this study to have shown a “protective” ETS effect. As pointed out in the Document (see page 7-30), the OR associated with exposure to husbands smoking only was 1.5 (table 5 of Coker *et al.*, 1992), while the OR associated with exposure to husbands’ smoking only and to parent and husbands’ smoking combined were 2.2 (we calculated this OR using data presented in table 5 of Coker *et al.*, 1992).

Gio Batta Gori, The Health Policy Center, for The Tobacco Institute

Nasal Sinus Cancer

1. Comment Summary: The Hirayama (1983) study partially accounted for only age and occupation of the husband, and found no association for active smokers. The Fukuda and Shibata study reports a greater risk for household exposure to ETS than for active smoking. Other studies report surprising “protective” effects for cigar and cigarette smokers. Brinton *et al.*, 1984 reported a risk estimate $RR = 0.72$, 0.3-1.6 95% CI, while Zheng *et al.*, 1993 reported an $OR = 0.6$, 0.3-1.2 95% CI.

The paper by Zheng *et al.* (1993) suggests a threshold of 30 daily cigarettes smoked over 25 years. A similar threshold for active smoking was repeatedly observed for cancers of the oral cavity, pharynx and larynx by Wynder *et al.* (1957), Keller (1967), and Martinez (1969). Since nonsmokers are subject to doses orders of magnitude below threshold doses for active smokers, the results of the ETS studies indicate massive confounding or reporting bias.

Response: The commenter discredits the Fukuda and Shibata study on the basis of their report of a greater risk for household exposure to ETS than for active smoking. The RR of 5.73 associated with greater than one smoker in the household was based on a small number of cases (n=9) and controls (n=5). We have noted the wide confidence interval for this point estimate in the Document (pg 7-27) and have presented a more stable risk estimate associated with any smoker in the household (RR=1.96, 95% CI=0.8-4.5; pg 7-27). This risk estimate associated with ETS exposure in the household is compatible with effects of active smoking in this study population: RRs of 2.5 to 4.6 were associated with different levels of active smoking among men in this study (Table 3 of Fukuda and Shibata, 1990).

The lack of a significant effect (as with the lower exposures in the Zheng *et al.*, study) does not indicate the existence of a threshold. As discussed in the document (Section 7.3.1.2), direct comparisons of risk estimates between ETS and active smoking are problematic for this type of cancer if the histologic type of tumor is not classified. The “protective” effects given by the commentator do not appear to be statistically significant. It is not clear whether the studies of active smoking and cancers of the oral cavity, pharynx, and larynx, are pertinent to the issue of ETS and nasal sinus cancer. Finally, studies on active smoking and nasal sinus cancers have shown up to a 5-fold increase in risk with heavy smoking, as indicated in Section 7.3.1.1.

Cervical cancer

1. Comment Summary: What could be the Draft’s meaning of suggestive evidence for a cervical cancer risk and ETS exposure when a possible association with active smoking is so doubtful and subject to the confounding of such numerous factors as alcohol intake, diet, illicit drug use, use of oral contraceptives, sexual behavior (multiple partners), HIV, human papilloma viruses 16/18, herpes simplex virus type 2, and more? Certainly the Draft compilers would agree that DNA adducts and nicotine/cotinine that might have come from ETS or other sources can be found in any tissue or excretion of exposed subjects. Would that be justifiable grounds to conclude that ETS exposure alone is the cause of any and all diseases?

Response: We have referenced six studies (and there are more) in Section 7.3.2.1 which have found an association between active smoking and cervical cancer, after adjusting for the confounding factors given by the commentator. The studies concerning ETS and cervical cancer are suggestive that ETS is a causative agent in the development of cervical cancer. However, since potential influence on the results by confounding variables cannot be ruled out completely, the ETS document concludes that the evidence is “suggestive” for causality, as defined in Section 1.4 of the document. The presence of tobacco constituents in cervical tissue indicates that these and other constituents have access to cervical tissue. While this fact alone does not necessarily establish cervical tissue as a target tissue, it does help address concerns about biological plausibility. As with any systemic toxicant, factors in addition to tissue accumulation operate to

determine the effect on a target tissue. Therefore, there will be tissues with appreciable levels of a toxicant that are relatively refractory to an adverse outcome.

2. Comment Summary: Slattery *et al.* (1989) report the incredible finding that the risk of cervical cancer is the same for smokers and ETS exposed nonsmokers, only to be contradicted by Cocker [sic] *et al.* (1992) who find little risk in nonsmokers lightly exposed to ETS, and a protective effect (OR = 0.4) for nonsmokers heavily exposed at home or at work. Hirayama (1981) did not control for known confounders and the author states that “[t]he husband’s smoking habits seemed to have no effect on their wives’ risk of developing other major cancers, such as cancer.....of the cervix”. The same paper reports that husband’s drinking habits protect wives from the risk of cervical cancer, despite the well-known close correlation of alcohol and cigarette consumption. The Draft’s arguments for a causal role of ETS exposure appear to lack any balance of a weight of evidence analysis (p. 7-32), and ignores more cautious considerations of an earlier OEHHA draft.

Response: The ETS document concludes that the evidence of cervical cancer from the positive studies mentioned above on ETS and the risk of cervical cancer are suggestive of causality. The suggestive category, as explained in Section 1.4, includes effects for which there appear to be an association with ETS exposure, but for which confounding factors cannot be completely ruled out. The document does not indicate a causal role for ETS in cervical cancer, as shown in Table ES.1.

Maurice LeVois and Maxwell Layard, Environmental Health Resources, for The Tobacco Institute

Nasal Sinus Cancer

1. Comment Summary: The claim that nasal sinus cancer is caused by ETS exposure is based on only 3 studies and the reported risk is improbably high in relation to active smoking risk. Active smokers are exposed to orders of magnitude greater ETS than are nonsmokers, yet the nasal sinus cancer risk is essentially the same. This is biologically implausible.

Response: This comment has been raised by another commentator and has been addressed in Comment #1, Gio Batta Gori for the Tobacco Institute, nasal sinus cancers.

2. Comment Summary: It is highly inconsistent for Cal/EPA to criticize the analysis by Layard of NMFS data concerning ETS and heart disease, claiming that the NMFS data suffer from “...information provided by next-of-kin...”, and that “...misclassification bias of ETS exposure cannot be ruled out...” Exactly the same NMFS data base, and essentially the same methods, were used by Zheng *et al.* (1993) for their ETS/nasal sinus cancer study, which Cal/EPA relies heavily upon as support for their inference that ETS causes nasal sinus cancer.

Response: Although the analyses conducted by Layard (1995) and by Zheng *et al.* (1993) both utilized the same database, i.e., the National Mortality Followback Survey (NMFS), we found the study conducted by Zheng *et al.* (1993) to be credible but that conducted by Layard (1995) to be seriously flawed. As detailed below, although both studies used the NMFS data, there are important differences in the two analyses.

First, the percent of eligible cases that was included by the two studies differed substantially. In the Layard (1995) study, there were a total of 2630 deaths due to ischemic heart disease that were available for selection. Of these, 1241 (549 males, 692 females, or 47%) were excluded in the analysis because the subject had never married, the marital status was not known, or the spouses' smoking habits were not known. The final case group was comprised of 1389 subjects (475 males, 914 females). Thus, nearly one-half of the eligible subjects were excluded for the above reasons. In contrast, in the Zheng *et al.* (1993) study, there were 168 deaths from nasal sinus cancer and 147 were included in the analysis; only 12.5% of the eligible case subjects were excluded. The possibility of selection bias is substantially greater in the Layard (1995) study, given the large percentage of subjects who were excluded.

Second, the causes of death among controls included in the Layard (1995) study were not described. The investigator presented only the causes of death excluded (cancers of the lung, mouth, pharynx, larynx, esophagus, pancreas, bladder, kidney, and cervix, cerebrovascular disease, and chronic obstructive lung disease). In contrast, Zheng *et al.* (1993) cited the causes of death they excluded among their control groups, including the exclusions used by Layard (1995) as well as other exclusions; more importantly, Zheng *et al.* (1993) presented the actual distributions of causes of deaths of their controls. Since a large number of malignant and non-malignant health endpoints are associated with the use of tobacco and alcohol, it is problematic that causes of death among controls were not described by Layard (1995).

Third, Layard (1995) described his study design as including ischemic heart disease death in all men aged 25-44 years and women aged 25-54 years, yet the mean age at death of the case and control groups appear completely inconsistent with this sampling design (as discussed in the response to comments on Chapter 8, see response to comment 3 of the Tobacco Institute).

For these reasons, the Layard (1995) study is seriously flawed and the results are not credible.

3. Comment Summary: Cal/EPA's estimates of risk for nasal sinus cancer is dominated by Japanese data, which is clearly inappropriate for extrapolation to cancer risks in the U.S.

Response: The studies, which include 1 American and 2 Japanese study groups, contained consistent positive associations that could not be reasonably explained by the presence of confounding factors.

Others

Stanley M. Greenfield

Comment Summary: The Hirayama (1983) report does not explain if the number of cigarettes smoked by the husband was limited to the number of cigarettes smoked in the wife's presence.

Fukuda and Shibata (1990) accounted only for number of smokers in the household, but the number of cigarettes smoked in the home was not characterized.

Zheng *et al.* (1993) do not present the number of cases or controls, nor do they present data on quantity of cigarettes smoked by spouses, although the text references it.

In conclusion, Cal/EPA requires specific statements of the limitations of the analyses performed by industrial and commercial firms within California when they submit risk assessments to Cal/EPA. Yet it appears that, for this ETS document, Cal/EPA has not followed its own procedures and recommendations.

Response: The exposure assessments for Hirayama *et al.* (1983, 1984) and Fukuda and Shibata (1990) have limitations. The assumption that increasing the number of cigarettes smoked per day would tend to also increase the exposure to passive smoke is reasonable, though clearly an exact measurement of the amount of passive smoke inhaled would be preferred. Alternatively, it is reasonable to conclude that an increasing number of smokers in a household would tend to increase the exposure to passive smoke in nonsmokers. The Zheng *et al.* (1993) study indicates the number of cases and controls for never smokers in Table 2 of their report. For the commentator's information, the reference to the relationship of the number of cigarettes smoked is also given in Zheng *et al.* (1993), on page 967.

The ETS document attempts to disclose all important limitations in its discussion of the studies. All studies contain limitations. It is OEHHA's judgment that the limitations in the studies on ETS and nasal sinus cancer do not explain the significantly positive effects observed.

Linda Stewart

Comment Summary: "Hirayama and Sandler did not account for "Known risk factors for breast cancer," their results were contradictory, their findings non-significant. It's a tossup as to which of these studies is the more absurd. Sandler is a case control study (of an indeterminant size) in which the smoking of the husband (of how many cigarettes? And how many within the home?) was associated with an increased breast cancer risk

among (but only among) premenopausal women, many of whom smoked, and with a confidence interval of...29.7! (CI = 1.6 - 31.3. The EPA itself discredits confidence intervals as narrow as 5.1. Post-menopausal women were not affected at all, and showed a slightly protective effect. (RR = 0.9). And then anomalies seem to abound. The upshot of Sandler's study is that smokers married to smokers are the safest women on earth (RR = 0.64). (Are we assuming they don't breathe?).

"Wasn't it Dr. Smith himself who concluded... 'The lack of an effect [on female smokers] of their own smoking, and the fact that such smokers are also themselves exposed to the effects of passive smoking, makes any relationship between exposure to others' smoking and breast cancer implausible' ".

The study by Moravia contains results that are not credible considering that the reported risks were higher for someone exposed to passive smoke 2 hours a day for 25 years compared with having smoked an average of 20 cigarettes a day for 20 years. In addition, it is unrealistic to expect 70 year old women to calculate the inhalations of 1929, 1937, or 1942.

Response: As stated in the document, Section 7.4.1.1, the studies on breast cancer contain results that are presently inconclusive. The document clearly states that the majority of the studies found no association, which also appears to be the opinion of the commentator. The limitations and discrepancies in the studies highlighted above are consistent with this conclusion.

A. Judson Wells

1. Comment Summary: This is a fine report, especially the Chapter on cardiovascular disease. The weakest section is 7.4.1 on breast cancer, which is covered first in the following comments.

Response: Comment noted.

2. Comment Summary: Section 7.4.1.1 fails to cover the active smoking result in Morabia *et al.* (1996) where, if the various exposure levels are combined, the OR would be 3.02 (95% CI = 1.9 - 4.8). Contrary to the statement in Section 7.4.1.2, Morabia's study was designed from the start "to determine the relation of active and passive smoking to breast cancer", not just the effect of ETS.

ETS is a powerful confounder in all of the earlier studies where all never smokers, including those passively exposed, were used as the reference category when considering the risk from active smoking.

It is possible to get an active smoking effect versus non-ETS exposed never smokers by subtracting the data in Table V from Table IV in the Smith *et al.* (1994) study, although the final result is OR = 1.47 (95% CI, 0.93 - 2.33), which is nonsignificant. The Smith

result is less statistically significant probably because they had so few never smokers who were exposed. All this needs to be explained in this section on active smoking.

Response: All previous epidemiologic studies on active smoking and breast cancer (and those cited in section 7.4.1.1) used all nonsmokers as the baseline comparison group. In contrast, in the study conducted by Morabia *et al.* (1996), the baseline group is nonsmokers not exposed to any ETS. We have now added a third paragraph in section 7.4.1.1 describing these results. However, unlike an exposure category such as nonsmokers, nonsmokers with no exposure to ETS (e.g., during childhood, adult life, at home, and outside the home) may be more subject to misclassification. This baseline group is likely to vary from study to study depending on the questions used to determine any ETS exposure. Thus, it may be more difficult to compare results study to study.

Tables IV and V of Smith *et al.* (1994) show the risks of breast cancer by passive smoking exposure for smokers and nonsmokers combined and in nonsmokers alone, respectively. Although one can calculate the effect of passive smoking in active smokers (by subtracting data from Table IV from those in Table V), we fail to see the rationale for such an analysis. Active smokers are exposed to passive smoking and it is difficult to interpret an effect of passive smoking in active smokers.

3. Comment Summary: The comment in Section 7.4.1.2 about the age of women in Hirayama (1984) needs to be corrected. The age ranges should be adjusted to be closer to 65 - 74, instead of 50 - 59, due to 10 years average additional life in the 16 years of followup, and for 5 years difference between husband's and wife's age. These would hardly be considered "younger women".

The comment on page 7-37 that they did not report their findings separately for nonsmokers is incorrect. Their data on ETS effects on never smokers are in their Table V.

Response: These corrections have been made to the document.

4. Comment Summary: Dr. Hirayama has provided data to me in 1988 indicating a breast cancer smokers' risk versus non-exposed never smokers of 2.03 (95% CI, 1.22 - 3.38). Though the explanation for the similar risks for active and passive smoking is not known, one hypothesis suggested by Dr. Hirayama is that there is a relatively small group of women (15-20%), who were very susceptible to breast cancer and who could develop tumors from almost any carcinogenic exposure, such that passive smoke exposure was about as good an initiator as active smoking, and that further exposure of either type would not make the result any worse. Others have hypothesized that nitrosamines are responsible for the high OR of passive smokers, or that active smoking protects against breast cancer by depressing estrogen levels. In summary, there is more evidence for the association between active and passive smoking and breast cancer than is presented in your writeup. The evidence for causality for breast cancer should be moved into the suggestive category in Table ES.1.

Response: We agree that the above hypotheses are interesting, and should be investigated. However, the hypotheses and the personal communication mentioned are not sufficient evidence to change the current weight of evidence classification for breast cancer and ETS. Should additional convincing peer-reviewed data on ETS and breast cancer incidence become available, a future re-evaluation may become necessary.

5. Comment Summary: The study by Pritchard *et al.* (Environ. Technol. Lett 1988;9:545-552) should be given attention. This paper showed that 70% of the tar in aged ETS evaporates into the gas phase. Apparently, the lung has no clearance mechanism for vapor phase deposits. Mainstream smoke, by contrast, consists mostly of large particles that deposit mostly in the mouth and larger airways, where most are cleared to the mouth and swallowed. This may help explain why the concept of cigarette equivalents is problematic.

Response: OEHHA thanks the commentator for suggestions on improving the ETS document. The mentioned references appear to be pertinent to the issue of cigarette equivalents. However, this issue does not impact the overall conclusions of the document.

6. Comment Summary: There are several references that should be included:

Chapter 3 does not reference a good paper on low birth weight by English *et al.*, Am. J. Public Health 1994;84:1439-1443.

Chapter 7, reference should be made to my discussion of compounds in the vapor phase of ETS, Environ. Int. 1991;17:382-385.

In Section 7.2.2 there is one new lung cancer/passive smoking study missing, namely, Schwartz *et al.* Am. J. Epidemiol. 1996; 144:554-562.

Response: OEHHA thanks Dr. Wells for these suggestions for improving the document, but after consideration, the first two references have not been included in the document. The study by Schwartz *et al.* has been briefly summarized in the final document.

Comment Summaries and Responses on Chapter 8: Cardiovascular Health Effects

Philip Morris

Philip Morris USA, submitted by Richard Carchman, Scientific Affairs

1. Comment Summary: The commenter finds that the draft “fails completely as an objective scientific evaluation of the relevant cardiovascular literature.” In the commenter’s view, the draft “summarizes, with little regard for scientific validity and methodologic flaws or relevance, a range of studies which only give the appearance of a scientific underpinning for OEHHA’s claims, but do not do so in substance.” The commenter believes that “OEHHA’s review and evaluation of the ETS/cardiovascular issue is, in fact, little more than a restatement of advocacy positions...”

Response: As discussed in the draft (Section 1.4), a weight of evidence approach was used to describe the body of evidence on whether or not ETS exposure causes a particular effect, including cardiovascular disease. Section 8.2 describes in detail the basis for the finding of a causal association of ETS exposure and risk of CHD, in terms of the findings of the published reports. The determination is based on the overall weight of evidence, and includes some residual uncertainties and lack of understanding of certain mechanisms; it represents a conclusion from the evidence, rather than a bias *a priori*.

2. Comment summary: The commenter considers the draft’s statements regarding a causal association between active cigarette smoking and CHD problematic, and states that the draft ignores or downplays inconsistencies and gaps in the available data. The commenter believes that the draft “implies, invalidly, that active cigarette smoking and ETS involve comparable exposures (except for quantity),...repeatedly relying on active smoking data in supporting its ETS claims.”

Response: As summarized in the draft (pg. 8-1), a causal association between active smoking and CHD is well established, as reported by the U.S. Surgeon General in 1983 and 1990. Evidence from case-control and cohort studies has clearly revealed a higher risk of myocardial infarction, sudden unexpected death, and other deaths from CHD in cigarette smokers than in nonsmokers. The data are generally supportive of a dose-response relationship in that the risks increase with increasing duration of smoking, increasing number of cigarettes smoked, and with depth of inhalation. The association seen with angina pectoris has not been consistently observed, although smoking clearly provokes angina pectoris, and risks of angina pectoris are elevated in smokers compared to nonsmokers in some studies; the association with smoking tends to be weaker for angina pectoris than for other heart disease endpoints. Other inconsistencies in the smoking literature are also examined briefly in the draft (pg. 8-25), such as the negative finding for uncomplicated angina pectoris in women reported in the Framingham study, which has been attributed to the low percentage of women who smoked in this

population, and to the fact that even among women who smoked, most were light smokers, and thus the study did not have the power to detect a significant association.

Data on active smoking are reviewed primarily in relation to considerations of biological plausibility of the association seen with exposure to ETS and risk of CHD. The relationship of active smoking and CHD provides evidence of biological plausibility for the association of ETS and CHD, given that both exposures occur due to the combustion of tobacco. The draft also reviews the epidemiologic literature with respect to numerous other criteria to determine whether the available studies support an inference of causality. Section 8.2 specifically addresses each of the criteria in turn, including the consistency of the association, statistical significance of the results, findings of dose-response, and control for confounding, among other issues.

3. Comment summary: The commenter considers the epidemiologic data to be “scientifically flawed and unreliable”, and the information on mechanism of action to be based on “scant and methodologically unsound data from laboratory animal and human clinical reports.” The commenter refers to the documentation of these weaknesses provided in the Philip Morris submission to federal OSHA in 1996 (which was attached to the submitted comments). The draft “does not give adequate weight to these flaws, despite frequently acknowledging them, and cannot be considered an objective evaluation of the data.”

Response: As noted by the commenter, the epidemiologic studies published to date had various limitations which were noted and discussed in the draft. Despite these limitations, the epidemiologic data, from prospective and case control studies conducted in diverse populations, in males and in females, in western and eastern countries, are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers. Strengths of the available studies are also noted, such as the advantage prospective studies have that information on smoking status and exposure to ETS was obtained prior to diagnosis of heart disease, minimizing selective recall bias, and the more detailed information on ETS exposure and from spouses as well as from other sources in some case-control studies. Data from clinical studies, discussed to elucidate various possible mechanisms for a causal association between ETS and heart disease, collectively show that deleterious effects seen following ETS exposure may account for both short-term and long-term effects of ETS exposure on the heart. Studies in animals provide information regarding the contribution of short term ETS exposure to the promotion of the atherosclerotic process. However, while of interest, such information on mechanism of action is not relied upon to support the inference of causality made on the basis of the epidemiologic data. Results from the epidemiologic, clinical and animal studies all point to an adverse effect of ETS exposure on risk of cardiovascular disease and thus strengthen the overall evidence.

4. Comment summary: Confounding stemming from spousal concordance of CHD risk factors is “[o]ne of the most significant methodological weaknesses...” “CHD risk profile differences associated with ETS exposure...and the resulting confounding in the

epidemiologic studies, were recognized by OEHHA.” The draft’s recognition of these issues is “inconsistent with its conclusion that the data support an independent relationship of ETS exposure with increased CHD risk.”

Response: The report acknowledges the limitations of the available studies, such as the fact that information on the established risk factors for CHD were not available in all studies, including two large cohort studies (Hirayama, 1984; Helsing *et al.*, 1988). The study conducted by Steenland *et al.* (1996) using the CPS II cohort included a large number of potential confounders in their analysis.

The concern about confounding due to spousal concordance of CHD risk factors is based on an assumption that nonsmokers with smoking spouses differ from nonsmokers with nonsmoking spouses in other lifestyle habits that are related to heart disease. There is, however, little evidence that this could have explained the observed findings in the studies of ETS and CHD. In the studies which presented data on other heart disease risk factors (blood pressure, cholesterol, body mass index) and dietary habits among nonsmokers stratified by the smoking status of their spouses (Garland *et al.*, 1985; Svendsen *et al.*, 1987; Humble *et al.* 1990; La Vecchia *et al.*, 1993), nonsmoking women married to nonsmokers and those married to smokers were generally similar in other risk factors for heart disease. More importantly, in the studies which presented relative risks adjusting for demographic factors only (i.e., age and sex), and relative risks adjusting for demographic factors and other CHD risk factors, the latter relative risks were not invariably lower after such adjustment (Garland *et al.*, 1985; Svendsen *et al.*, 1987; Butler, 1988; Humble *et al.*, 1990). A specific (or uniform) direction in change of the OR with adjustment (either increase or decrease) would be expected if confounding was the explanation for the effect on CHD risk associated with ETS exposure.

5. Comment summary: The commenter objects to the draft’s statement: “The association between ETS and CHD is also consistent with the active smoking and CHD association in that the relationship is stronger for fatal CHD outcomes than for nonfatal outcomes and angina.” The commenter believes the “data do not support an association of ETS exposure with cardiovascular symptoms, such as angina”, and finds the draft’s report of an elevated risk of angina in the high ETS exposure group in the Hole *et al.* study as “curious” given the draft’s mention elsewhere that “active smoking does not have a consistent relationship with angina risk”.

Response: While the association seen with angina pectoris and active smoking has not been consistently observed, smoking clearly provokes angina pectoris, and risks of angina pectoris are elevated in smokers compared to nonsmokers in some studies. There is little information on the effect of ETS on cardiovascular symptoms such as angina. Thus it is of interest that in one study with information on angina (Hole *et al.*, 1989), prevalence of angina increased in relation to exposure to ETS. Of the various CHD endpoints, death from CHD, nonfatal myocardial infarction, and angina pectoris, those with angina pectoris have less severe CHD manifestations. Moreover, there are different forms of angina pectoris and thus the diagnosis of angina may be less sensitive and less specific

than the other CHD endpoints. Variation in the strength of association between active smoking and angina pectoris may be explained in part by these reasons.

6. Comment summary: The commenter cites reports of the Surgeon General with respect to the increased risk of CHD death in smokers relative to nonsmokers (70%) and contrasts that with the draft's acceptance of a 30% increased risk for nonsmokers exposed to ETS, stating that the ETS-related risk "makes no biological or statistical sense".

Response: The question of whether the magnitude of the effect of ETS on CHD is consistent with the active smoking relationship with CHD is discussed in the draft (pages 8-25 to 8-26). The draft indicates that an increased risk of about 30% for ETS exposure and CHD estimated from the available studies is believable relative to the two- to three-fold risk seen in more recent studies of active smokers. While these relative risks are considerably higher than those estimated from earlier studies of active smokers, the higher risks for CHD in more recent cohorts may be due to the earlier age of smoking initiation, deeper inhalation during smoking, and other differences in smoking behavior. Moreover, the risk estimates for studies of active smoking and heart disease use as a comparison group all nonsmokers, which includes those with and without exposures to ETS. Because the risk estimates in active smoking and ETS studies use different baseline comparison groups, the numerical values are not directly comparable.

7. Comment summary: The commenter refers to the analyses of the "previously unpublished data from the American Cancer Society [CPS I and CPS II] and the National Center for Health Statistics [NMFS]" as indications of publication bias, and the draft's treatment of these "indicates a seriously biased interpretation of the literature." The commenter elaborates on the findings of the studies published by Layard (1995) and LeVois and Layard (1995), who utilized these data.

Response: The review in the draft of the studies mentioned by the commenter can be found on pages 8-12 to 8-21; they are also discussed as part of the collective evidence (Section 8.2). Methodological limitations of the Layard (1995) and LeVois and Layard (1995) analyses, which provide null results, are summarized here briefly.

Limitations of the case-control study by Layard (1995), which uses data from the 1986 NMFS cohort, include reliance exclusively on information provided by next-of-kin of subjects who had died, and failure to specify causes of death for control subjects beyond indicating the excluded causes of death, raising concerns regarding misclassification bias of ETS exposure and selection bias of controls. Among other problems with the Layard (1995) study are the apparent lack of matching for age at death or race: cases were older (mean age at death: men, 72.6; women, 78.2) than controls (64.8, men; 71.9, women), and a higher percentage of cases (74.9%, men; 73.9% women) than controls (68.2%, men; 68.4%, women) were white.

LeVois and Layard's (1995) analysis of the CPS-I cohort, which included a large number of CHD deaths, was limited by the lack of clarity on selection of subjects for analysis; for

example, it is unclear what percent of subjects were excluded because their own smoking habits were missing or because the smoking habits of spouses were unknown. LeVois and Layard's (1995) analysis of the CPS-II cohort, after adjusting for age and race, found no association between any ETS exposure from spouses and risk of CHD mortality in men or in women; however, the emphasis of LeVois and Layard on 'any' (*i.e.*, current and former) ETS exposure from spouses and exposure from spouses who were former smokers, strongly biased the results toward the null. In both men and women, there was some increase in risk when amount smoked by spouses was considered. Almost all the risk ratios (RRs) associated with each exposure category (based on amount currently smoked by spouses) were above 1.0 for women in both CPS I and CPS II and for men in CPS II. In fact, in the CPS II analysis, five of the six RRs associated with varying amounts smoked by spouses were above 1.13. These RRs by amounts currently smoked by spouses suggest that the RR for any exposure to current smokers is above 1.0 (RRs associated with any current smoke exposure were not presented and could not be computed on the basis of the data presented). As pointed out by Steenland *et al.* (1996) and Glantz and Parmley (1996), ETS exposure may have both acute and chronic effects on the heart. The effect of exposure from former smokers may be negligible, similar to the rapid reduction in heart disease risk seen among active smokers upon cessation of smoking.

The issue of publication bias has been previously raised and considered.

8. Comment summary: The commenter finds the draft's review of the analysis of the CPS II data by Steenland *et al.* to be "a prime example of its biased approach to the literature," and believes this analysis "does not refute the previous analysis... by LeVois and Layard (1995)." The commenter specifies Steenland *et al.*'s analysis of "a portion of the data examined by LeVois and Layard (1995)" and Steenland *et al.*'s more narrow analysis of only "those nonsmokers married to current smokers" as evidence of "data-dredging". The exclusion of those married to former smokers (but not currently exposed), the commenter considers to be arbitrary.

Response: Steenland *et al.*'s (1996) analyses of the CPS-II cohort differed methodologically from those of LeVois and Layard (1995), and Steenland *et al.* (1996) did report statistically significant results. The study by Steenland *et al.* (1996) presents results from four analyses of the CPS-II cohort, three of which dealt specifically with ETS exposure from spouses; the fourth analysis investigated the effects of ETS exposure at home, at work, and in other settings. The first analysis was conducted only among those married individuals with spouses also enrolled in the CPS-II study, and for whom there were valid dates of marriage and sufficient data on smoking cessation to indicate whether the spouses had smoked during marriage. The second, third and fourth analyses utilized specified subsets of eligible subjects derived from the first analysis. Small increased risks for CHD mortality in men and women in association with current exposure to spouses' smoking were found in each of the analyses, with statistically significant results only in nonsmoking men. There was, however, no association between risk of CHD mortality in nonsmoking men and women and being married to spouses who were former smokers.

The fourth analysis found small elevated risks associated with all sources of ETS exposure, although only the association between CHD risk in nonsmoking men and ETS exposure at home was statistically significant.

The differences in Steenland *et al.*'s (1996) findings and those reported by LeVois and Layard (1995) are noteworthy given that both analyses utilized data from the CPS II study. The size of the relevant study population and the number of CHD deaths included by Steenland *et al.* (1996) differed from those included by LeVois and Layard (1995). In contrast to the detailed description of the inclusion and exclusion criteria presented by Steenland *et al.* (1996), LeVois and Layard (1995) provided few details regarding their study methods. Differences in the follow-up period, in the definition of spousal smoking or other criteria for inclusion and exclusion may have contributed to the differences in these two reports. As noted in the response to the previous comment, exclusion of former smokers is not arbitrary but reflects an understanding of the literature on tobacco smoke and CHD; a rapid reduction in heart disease risk is seen among active smokers upon cessation of smoking, and a similar effect of cessation of exposure to ETS may occur.

9. Comment summary: The commenter reviews aspects of Steenland *et al.*'s analysis and results, including the "gender inconsistency" of the statistical findings, the lack of control for heart disease risk factors (cholesterol and blood pressure levels), the influence of potentially inaccurate self-reports of smoking status, and the lack of a consistent dose-response trend or of an association with workplace exposure to ETS. He also notes that Steenland, in a recent publication, discussed ETS exposure in the workplace "as a 'suspected' risk factor for heart disease"; Steenland also listed reasons why the association is less well established than that of ETS exposure and lung cancer.

Response: The fact that the ORs were not identical in the men and women in the Steenland *et al.*'s study should not be equated with gender inconsistency. Steenland found slightly higher risk estimates in men than in women and in each of the four analyses, but elevated risks were observed in both genders. Serum cholesterol and blood pressure levels were not available for adjustment in this study. However, many established risk factors for heart disease were adjusted for (see pg 8-14 for description) in the ETS-heart disease analysis.

Steenland, as quoted by the commenter, gave reasons for the difference in the association seen for workplace exposure and CHD as compared to lung cancer: "(1) the number of studies is smaller, (2) heart disease is less strongly related to mainstream smoking than lung cancer, and (3) numerous well-known risk factors for heart disease could potentially confound the small excess risk observed." As summarized in the draft, information on risk of CHD in relation to ETS exposure from workplace or other settings is available in a few studies, with one study finding that any effect of workplace ETS exposure was small and was not statistically significant (Steenland *et al.*, 1996), while another (He *et al.*, 1994) found exposure to ETS at work significantly increased the risk of CHD in women; these latter study subjects had full time jobs and thus had the opportunity to be exposed at work. Most of the other studies had limited ability to investigate the role of workplace

ETS exposure since only small numbers of subjects had jobs outside the home. The relationship of active smoking and CHD, and the possible confounding by other CHD risk factors, are also discussed in the draft. Moreover, the draft's conclusion, that "the epidemiologic data...are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers" does not mention workplace exposure.

Issues regarding self-reported smoking status, dose-response, and results of studies of workplace exposure have been previously raised and considered.

10. Comment summary: The failure of the epidemiologic studies of CHD and ETS to fully address factors that impact CHD risk such as obesity and diet, physical activity, socioeconomic status, gender, and responses to stress make the conclusions regarding the association "scientifically unwarranted." The commenter emphasizes the growing literature on stress and personality factors, noting that these also need to be considered in exercise performance studies.

Response: Although many factors may be related to CHD, a factor is a confounder only if it is associated with CHD, associated with exposure to ETS, and is not an intermediate in the causal pathway between exposure and disease. In the case of dose-response relationships, the confounder has to be associated with exposure and disease in the same dose-response fashion. While confounding by the factors mentioned by the commenter is theoretically possible, it is not likely.

11. Comment summary: The commenter objects to the draft's characterization of the association between active smoking and CHD as "well established"; he argues that the development of CHD "is poorly understood, as are the mechanisms by which particular risk factors might play a role." Data on "infective mechanisms of atherogenesis" are mentioned, including some which indicated a possible causal role of cytomegalovirus in CHD. The draft's failure to address this and other facets of the "complexities in the cardiovascular literature" in the discussion of mechanism of action of ETS exposure is problematic.

Response: The commenter's suggestion that active smoking and CHD is not well established is difficult to reconcile with the mountainous evidence in support of the association. If this amount of information can be ignored by the commenter, why would the same person be interested in the alternative hypothesis (i.e., infective mechanisms) when there is little evidence which is much less well understood?

12. Comment summary: As for the information on mechanism of action which is included, "the data on platelets are inconsistent", "other clotting-related blood parameters, such as fibrolytic activity, are related to measurements of stress", and "preliminary data" on nitric oxide (NO) are used "to speculate about how they could explain [the draft's] predetermined conclusion that cigarette smoking and ETS exposure cause atherosclerosis." In addition, the cited animal studies are "fundamentally flawed and are

inconsistent with active smoking studies”, and are limited to the work of programs at two universities (University of California at San Francisco and New York University).

Response: The draft’s conclusion is based on a weight-of-evidence consideration of the epidemiologic studies, and the results from the clinical and animal studies serve as corroborative data.

Dennis Frate for Philip Morris

1. Comment Summary: The commenter provides background information regarding research design, research methods, and statistical analysis/interpretation of epidemiologic studies. With respect to CHD, he emphasizes the multifactorial nature of the disease, and the need for complex etiological models, as well as representative samples; he also stresses the critical nature of measurements of the phenomenon in question. He suggests that, “when developing a causal or predictive model multivariate statistical techniques are more appropriate [than the use of a probability level of $p < 0.05$]; the relative contribution of an independent variable to the dependent variable is of critical importance.”

Response: The authors of the draft are familiar with the statistical and epidemiologic concepts described by the commenter.

2. Comment summary: The commenter examines in turn each of the 17 epidemiologic studies reviewed in the chapter on cardiovascular health effects, with a focus on the extent to which the draft’s summary of each study discusses methodological issues and problems raised by the study. The commenter expresses the concern that in cases where “the results did not fit the ‘desired’ outcome of the reviewers, the methodology was criticized,” but that studies with other results had flaws which were not adequately discussed. The commenter also makes note of whether each study provides information which “can contribute to a predictive model...”.

Response: As discussed in the draft (Section 1.4), a weight of evidence approach was used to describe the body of evidence on whether or not ETS exposure causes a particular effect, including cardiovascular disease. Section 8.2 describes in detail the basis for the finding of a causal association of ETS exposure and risk of CHD, in terms of the findings of the published reports. The determination is based on the overall weight of evidence and includes some residual uncertainties and lack of understanding of certain mechanisms; it represents a conclusion from the evidence, rather than a bias *a priori*.

3. Comment summary: In addition, two studies are said to be missing from the chapter, which should be included: the study on publication bias by LeVois and Layard, and a study by Gio Gori entitled “Environmental tobacco smoke and coronary heart syndromes: absence of an association”.

Response: The study by LeVois and Layard (1995) is one of the 17 studies reviewed in the draft. The issues (including those raised by Dr. Gori) of the relevance of the data on

mechanism of action and animal studies, and the risk of ETS exposure compared to that of active smoking, have been previously raised and considered (see Appendix A, pages A-43 to A-48). Specific issues raised by Dr. Gori are addressed in the response to the comments Dr. Gori submitted.

4. Comment Summary: The commenter indicates that, in his opinion, “No definitive conclusion can be drawn about the reported association between ETS and CHD until higher quality studies are designed and conducted. It is scientifically inappropriate for any individual or organization to conclude a causal link at this time based on the available evidence.”[emphasis in original]

Response: As detailed in the draft, the evidence does support an inference of causality. Section 8.2 specifically addresses criteria with respect to the body of evidence relevant to the association between ETS exposure and risk of CHD, and indicates what was found. For example, consistency of the association and statistical significance: 14 of the 17 studies epidemiologic studies found an increased risk of CHD, and this increased risk was statistically significant in five studies and in one gender group in two additional studies; all three of the studies (Lee *et al.*, 1986; Layard, 1995; LeVois and Layard, 1995) which did not find an association had methodologic limitations, such as the inclusion of spouses who were former smokers in the exposed group, when there is some evidence that only current ETS exposure may influence risk of CHD.

Daniel Lackland for Philip Morris

1. Comment Summary: The conclusions of the report “do not appear to be based on the appropriate interpretation of the epidemiological studies referenced.” “Control and/or adjustment for the confounders associated with the traditional assessment of cardiovascular disease” is a concern to the commenter, and he lists “blood pressure, cholesterol and sub-fractions, body size, cigarette smoking and diabetes”, as well as secondary considerations including “blood chemistries...familial history, hormonal levels, as well as dietary intake and behaviors.” The commenter notes that “[a]lthough limitations of the various epidemiologic studies are mentioned, they are not adequately considered in the conclusions.”

Response: The report acknowledges the limitations of the available studies, such as the fact that information on the established risk factors for CHD were not available in all studies, including two large cohort studies (Hirayama, 1984; Helsing *et al.*, 1988). The study conducted by Steenland *et al.* (1996) using the CPS II cohort included a large number of potential confounders in their analysis. A concern is that nonsmokers with smoking spouses may differ from nonsmokers with nonsmoking spouses in other lifestyle habits that are related to heart disease. There is, however, little evidence that this could have explained the observed findings. In these studies, which presented data on other heart disease risk factors (blood pressure, cholesterol, body mass index) and dietary habits among nonsmokers stratified by the smoking status of their spouses (Garland *et al.*, 1985; Svendsen *et al.*, 1987; Humble *et al.* 1990; La Vecchia *et al.*, 1993), nonsmoking women

married to nonsmokers and those married to smokers were generally similar in other risk factors for heart disease. More importantly, in the studies which presented relative risks adjusting for demographic factors only (i.e., age and sex), and relative risks adjusting for demographic factors and other CHD risk factors, the latter relative risks were not invariably lower after such adjustment (Garland *et al.*, 1985; Svendsen *et al.*, 1987; Butler, 1988; Humble *et al.*, 1990).

2. Comment summary: “Potential inaccurate and poorly defined measured exposures of ETS” is also of concern to the commenter. He believes that “more accurate levels of ETS can be determined. For example,...[using] direct measurement instruments to monitor indoor air...Newer systems using personal monitors would seem to be even more appropriate.”

Response: This issue, which is not specific to assessing ETS exposure in relation to cardiovascular effects. This issue has been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses. (see page A-42).

3. Comment Summary: The commenter considers the draft’s summary of each of the studies reviewed and suggests additional critiques of the methods and findings (primarily in relation to the issues noted in comments 1 and 2), although some study summaries are judged positively, such as “appropriately describes the limitations and bias...”and “This is a reasonably designed and described study.”

Response: Although the commenter and other reviewers might choose to emphasize study findings differently, the summaries provided are objective reviews of the studies.

4. Comment summary: “The interpretations and conclusion in this draft of the report are preliminary and should not be considered the basis for regulation or policy. Rather, this report might be considered as a prompt for a well-designed study...”

Response: As detailed in the draft, the epidemiologic data, from prospective and case control studies conducted in diverse populations, in males and in females, in western and eastern countries, are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers. The draft acknowledges that further studies of the association could provide important information. For example: there is some suggestion that the association between active smoking and CHD may be stronger in younger subjects than in older subjects (although in some studies, the difference in relative risks by age was only apparent among the very heavy smokers), and two studies reviewed in the draft presented findings on ETS and CHD by age group. In one study, there was an apparent effect in the younger age group (25-44 years) and in the older age group (65+) (Helsing *et al.*, 1988). In another study (Steenland *et al.*, 1996), the association between risk of CHD mortality and exposure to spouses seemed to be more apparent for subjects aged < 65 years old. Future studies should monitor age-specific effects and cohort effects of ETS exposure on risk of heart disease.

Zadok Ruben, Patoximed Consultants, for Philip Morris

1. Comment Summary: The difference between effect and adverse [functional impairment] effect should be considered.

Response: The authors of the OEHHA report are familiar with this debate, which has been going on as long as the modern science of toxicology, and took these considerations into account in reaching their conclusions.

2. Comment summary: Peer-reviewed papers were given greater weight than other written sources and comments.

Response: The OEHHA document does give attention to non-peer-reviewed sources where appropriate, and where these contribute information not available elsewhere. However, in accordance with California risk assessment guidelines, peer-reviewed sources are invariably preferred when available. In particular, non-peer-reviewed sources cannot be regarded as representing that a particular hypothesis or interpretation of data has general support among the scientific community.

3. Comment summary: Comments on the scientific approach to exposure to ETS: definition of thresholds, and measurement of ETS exposure and constituents.

Response: As noted by the commentator, these issues were raised in earlier comments, and considered. OEHHA agrees that not all the variables and uncertainties have been completely resolved. Although the commentator's personal judgment appears to suggest otherwise, OEHHA has determined that the weight of evidence supports the conclusion that ETS causes various adverse health effects, including cardiovascular effects.

4. Comment Summary: Excess weight is given to epidemiological investigations.

Response: In accordance with California risk assessment guidelines and with general scientific practice, epidemiological evidence in humans, when available, is always regarded as the primary and most influential evidence of human health effects.

5. Comment Summary: Death certificate data are an unreliable source of information for epidemiological studies.

Response: Inaccuracies in this source of data are well known to epidemiologists, including the authors of OEHHA's report. These records are widely and effectively used in epidemiological studies in spite of the acknowledged imperfections. Although problems undoubtedly exist, cardiovascular diseases are commonly diagnosed and widely understood as causes of mortality. The specific strengths and weaknesses of the data

sources used in studies considered in the ETS report are described, considered and taken into account in the overall evaluation.

6. Comment Summary: Intimal-medial thickening of carotid arteries was assumed to provide evidence for atherosclerosis.

Response: In line with the intentions of the study authors, the effect on arterial wall thickness is used as a marker for processes which are generally believed to be associated with atherosclerosis.

7. Comment Summary: Presence of endothelial “carcasses” in circulating blood as evidence for endothelial damage.

Response: The report cites experimental observations of increased epithelial cells and anuclear carcasses, which are most reasonably interpreted as indicating increased desquamation of endothelial cells, in active and passive smokers.

8. Comment Summary: Alterations in fibrinogen blood levels and increased platelet sensitivity to aggregation are cited as evidence for toxicity by ETS.

Response: The report cites epidemiological and experimental evidence that both active and passive smoking may affect fibrinogen blood levels and increased platelet sensitivity to aggregation. OEHHA describes the hypothesis that changes in these parameters may contribute to the experience of cardiovascular disease in such persons. The importance of these parameters is widely accepted in the scientific and medical community, and is used as the rationale for routine clinical treatments as well as scientific investigations.

9. Comment Summary: Changes in lipoprotein profiles were used as evidence for toxicity by ETS.

Response: The report cites epidemiological evidence that both active and passive smoking may affect lipoprotein profiles. OEHHA describes the hypothesis that changes in these parameters may contribute to the experience of cardiovascular disease in such persons. The importance of these parameters is widely accepted in the scientific and medical community, and is used as the rationale for routine clinical treatments as well as scientific investigations.

10. Comment Summary: Some comments to the previous draft were inadequately covered.

Response: Some comments are expanded by explanations in the current series. OEHHA has read and acknowledged all the comments, but has not identified any information therein which would lead to a re-evaluation of the overall conclusion of the report.

11. Comment Summary: The report shows an overall bias toward proving adverse effects of ETS.

Response: OEHHA's conclusion is that ETS exposure causes adverse effects on the cardiovascular and other systems. This is based on the overall weight of evidence, including some residual uncertainties and lack of understanding of certain mechanisms. This determination represents a conclusion from the evidence, rather than a bias *a priori*.

R.L. Tweedie, Colorado State University, for Philip Morris

1. Comment Summary: The commenter provides a 70-page manuscript (Mengerson KL, Merrilees MJ, Tweedie RL, entitled "Environmental tobacco smoke and ischaemic heart disease: a case study in applying causal criteria", also noted to be "Technical report 97/8") which he indicates has been submitted for publication. He suggests that it be added to the material being addressed in the draft.

Response: The manuscript reviews the same literature as that reviewed in the draft, and has not been published; it is considered as part of the comments submitted but will not itself be added to the draft. As noted in the manuscript's acknowledgements, "Some of this research was carried out while preparing an evaluation of the NH&MRC Draft Report (1995) [National Health and Medical Research Council, *Draft Report of ...the working party on the effects of passive smoking on health*, Canberra [Australia]], for which funding was provided by the Tobacco Institute of Australia..." Much of the manuscript addresses a review of the literature using Bradford Hill criteria, apparently following an approach used in the NH&MRC Draft, and does not specifically address the review in OEHHA's draft.

2. Comment summary: The commenter believes that the conclusions of the chapter "clearly fit" the category of "suggestive evidence of a causal association" rather than "causally associated with ETS exposure". His manuscript reviews the same literature as is reviewed in the draft with respect to CHD, and concludes that "the association between ETS and CHD for the general population is, at best, weak." He notes that the draft suggests that the data support a stronger association between ETS and CHD for those persons with pre-existing heart disease, which is a conclusion reached by him and his colleagues (Mengerson *et al.*) in their manuscript.

Response: The draft's conclusion, as stated on pg. 8-36, is that "In summary, the epidemiologic data, from prospective and case control studies conducted in diverse populations, in males and in females, in western and eastern countries, are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers." The commenter and his colleagues may have reached some conclusions that are shared by the draft, but as he indicates, the overall conclusion is at odds with that of the draft.

3. Comment summary: The commenter has submitted, in an appendix, a consideration of the data considered under Section 8.3 of the draft, highlighting specific scientific considerations “which need to be addressed in seeking to judge the strength of the data and whether or not there is support for a causal link between ETS and CHD; much of [Appendix I] is based on the material in [the Mengerson *et al.* manuscript].” There are many flaws in the biological work, and many cases where the results do not bear the interpretation given to them in the draft. In the commenter’s view, the draft “is not a critical analysis of the data; rather the data sets and conclusions by authors are generally accepted without further evaluation...”

Response: The introduction to Section 8.3 explains that the purpose of the review of the clinical data is to identify the mechanisms whereby exposure to ETS increases the risk of CHD in nonsmokers, and to understand reasons for the relatively large effects of ETS on heart disease in nonsmokers compared to the magnitude of the effect of active smoking on heart disease. The draft then summarizes several processes that have been proposed to contribute to the clinical manifestations of myocardial infarction, particularly with respect to data relevant to the effects of ETS on these processes. However, the draft’s conclusion of causal association between ETS exposure and CHD is based on a weight-of-evidence consideration of the epidemiologic studies, and the results from the clinical and animal studies serve as corroborative data.

4. Comment Summary: The commenter provides detailed comments on several specific topics in Section 8.3, including:

- With respect to internal and common carotid wall thickness, the commenter notes that the draft considers the most important papers on this topic, but objects to inferences in the draft that increased wall thickness in ETS-exposed individuals has significance in terms of health risk.
- Whether the magnitude of impairment of endothelium-dependent vasodilatation caused by ETS exposure initiates or promotes development of atherosclerosis or compromises blood flow has not been established.
- Regarding exercise tolerance, that “[t]he conclusions in the OEHHA draft are not, in reality, substantially different from those in [the manuscript by Mengerson *et al.*] but the presentation...suggests that the reduced exercise tolerance occurs in all persons and is deleterious for all persons. The data do not support such strong statements.”
- On lipid profile, the commenter indicates that the draft omits “at least two relevant papers”, and believes that the conclusions in the draft are “too strong” given the quality of the evidence.
- Although the commenter believes that the data reviewed in the draft, “in general...support the conclusion” regarding effects on platelets of nonsmokers exposed to ETS, he finds no mention of the individual variability of this effect, and believes “there is no known deleterious impact of [such an effect], unless there is existing CHD.”
- “[I]t is not clear what [the] changes [seen in animal studies] represent in terms of the human condition.” The draft “does not provide a critical analysis of these studies...”

Response: Although essentially the same data are reviewed by the commenter in his attachments as are reviewed in the draft, in many cases the conclusions reached differ. In other cases, the commenter's interpretation of statements in the draft indicates a misunderstanding of the discussion of the data; for example, with respect to exercise tolerance, the strength of the draft's statement that "data also suggest that even among healthy subjects, [ETS] exposure may similarly impair exercise tolerance, although to a lesser extent", seems to be misconstrued in the commenter's characterization of the draft's conclusions. The papers mentioned by the commenter which are not included in the review of clinical data on lipid profile are animal studies; one of these is summarized in the section of the draft which addresses such studies. As mentioned above [see response to comment 3], the purpose of Section 8.3 is to identify possible mechanisms for the effects, rather than to prove the nature of the association; some of the differences in conclusion appear to be due to this difference of intention in reviewing the data.

5. Comment summary: In the review of the epidemiologic studies, the commenter believes that the draft reports inaccurate and misleading data, "data are rounded invalidly", "there is consistent over-stating and biased representation of negative results". Referring to studies included in the manuscript by Mengerson *et al.*, the commenter notes that "several studies are included in [the manuscript] that do not appear..." in the draft.

Response: All attempts have been made to ensure that the information in the draft is accurate. Although the commenter does not specify which studies are missing, a comparison of tables in the manuscript and the draft allows identification of one abstract presented at a meeting and another published in a periodical, and two unpublished dissertations cited in the manuscript, all of which are noted as "Not published in refereed journal". The draft focuses on studies which have appeared in the peer-reviewed literature,

6. Comment summary: The commenter finds "no plausible dose-response in the collection of studies..." and that the draft misrepresents the evidence for trends in the data, citing the discussion of the results of Steenland *et al.* as an example. The commenter objects that "[t]here is no real attempt made at combining information to get an overall picture of the relative risk even though this is required for valid calculations of attributable risks."

Response: The draft reviews the evidence collectively (see Section 8.2), including the information on dose-response trends, and identifies a best-estimate of relative risk associated with CHD. As noted above, although essentially the same data are reviewed by the commenter in his attachments as are reviewed in the draft, in many cases the conclusions reached differ.

7. Comment Summary: The commenter believes that publication bias is present in the data set, and provides in the manuscript an estimate of the relative risk which factors in

studies with null results, and suggests that this revised estimate should be used in calculating attributable risks.

Response: The issue of publication bias has been previously raised and considered. While the estimate provided in the commenter's manuscript, which relies on some form of meta-analysis and includes the non-peer-reviewed studies indicated above [see response to comment 5] may be of interest, the estimate of risk used in the draft is consistent with the findings in the peer-reviewed literature. One interesting aspect of their analysis is that, despite a downward shift in the estimate and its associated confidence interval, the estimate for CHD morbidity "with...publication bias" included is statistically elevated: as shown in Figure 6 of the manuscript, the confidence interval excludes 1.0.

8. Comment summary: The commenter presents alternative conclusions regarding criteria used in evaluating the epidemiologic studies, including:

- a) Strength of association: "the reported relative risk are not strong enough..."
- b) Dose-response: "there is limited support for a biological gradient (dose-response)..."
- c) Consistency of association: "although the reported relative risks are generally raised...the effect is not consistent in the sense of this criterion."
- d) Specificity of association: "there is no demonstrated specificity of magnitude, ...exposure,...and...of response." The commenter suggests that some of the alternative explanations for increased risks of CHD could account for much of the observed increase in relative risk.

The manuscript explores these issues in greater detail than is presented in the comments which address the OEHHA draft.

Response: As noted above, although essentially the same data are reviewed by the commenter in his manuscript as are reviewed in the draft, in many cases the conclusions reached differ.

The Tobacco Institute

The Tobacco Institute, submitted by Clausen Ely of Covington and Burling, attorneys

1. Comment Summary: "The draft report does not employ objective criteria for determining whether ETS exposure causes cardiovascular disease." Also, "OEHHA does not adequately explain the basis for its judgement..., does not respond to comments refuting that judgement and fails to reconcile its conclusion with the actual findings of the published studies."

Response: As discussed in the draft (Section 1.4), a weight of evidence approach was used to describe the body of evidence on whether or not ETS exposure causes a particular

effect, including cardiovascular disease. Section 8.2 describes in detail the basis for the finding of a causal association of ETS exposure and risk of CHD, in terms of the findings of the published reports.

2. Comment summary: “OEHHA’s own findings fail to support a causal association between ETS exposure and cardiovascular disease.” Using criteria regarding “the consistency of association, statistical significance of study results, strength of association, degree of dose-response relationship, and potential bias and confounding, the available epidemiologic studies fail to support an inference of causality...”, as illustrated by selected findings appearing in the draft.

Response: As detailed in the draft, the evidence does support an inference of causality. Section 8.2 specifically addresses each of the criteria listed by the commenter with respect to the body of evidence relevant to the association between ETS exposure and risk of CHD. For example, consistency of the association and statistical significance: 14 of the 17 studies epidemiologic studies found an increased risk of CHD, and this increased risk was statistically significant in five studies and in one gender group in two additional studies; all three of the studies (Lee *et al.*, 1986; Layard, 1995; LeVois and Layard, 1995) which did not find an association had methodologic limitations, such as including spouses who were former smokers in the exposed group, when there is some evidence that only current ETS exposure may influence risk of CHD.

3. Comment Summary: “Epidemiologic studies published since the original draft ETS/CHD chapter do not support a causal relationship between ETS exposure and cardiovascular disease.” “...Layard (1995), Layard/LeVois (1995) and Steenland (1996), provide powerful and consistent evidence of a lack of association between spousal ETS and CHD.” The draft “mischaracterizes the Layard/LeVois ETS/CHD studies, essentially ignores the large CPS I and NMFS cohorts, and claims that there are significant differences between the Layard/LeVois and Steenland analyses of the CPS II cohort when, in fact, both studies found no statistically significant association between ETS exposure and CHD risk.”

Response: Each of the studies mentioned by the commenter is reviewed in detail in the draft (see pages 8-12 to 8-21) and discussed as part of the collective evidence (Section 8.2). The Layard (1995) and LeVois and Layard (1995) analyses, which provide null results, are methodologically limited (see below). Steenland *et al.*’s (1996) analyses of the CPS-II cohort differed methodologically from those of LeVois and Layard (1995), and Steenland *et al.* (1996) did report statistically significant results (see below). As discussed above, despite some studies which are not supportive, the overall weight of evidence does support a causal association.

Also of interest: As summarized in the final document, Kawachi and coworkers (1997) at Harvard University investigated the association between exposure to ETS and risk of CHD using the Nurses’ Health Study, a cohort which was established in 1976 and included 121,700 female nurses. Compared to nonexposed women, those reporting

occasional exposure to ETS had a multivariate adjusted RR for total CHD of 1.56 (95% CI=0.93-2.68), while those reporting regular exposure had a RR of 1.97 (95% CI=1.11-3.28). In this study population, exposure to ETS was associated with increased risks of both nonfatal MI and fatal CHD events. ETS exposure, both at work and at home, were associated with the increase in risk.

Limitations of the case-control study by Layard (1995), which uses data from the 1986 NMFS cohort, include reliance exclusively on information provided by next-of-kin of subjects who had died, and failure to specify causes of death for control subjects beyond indicating the excluded causes of death, raising concerns regarding misclassification bias of ETS exposure and selection bias of controls. Among other problems with the Layard (1995) study are the apparent lack of matching for age at death or race: cases were older (mean age at death: men, 72.6; women, 78.2) than controls (64.8, men; 71.9, women), and a higher percentage of cases (74.9%, men; 73.9% women) than controls (68.2%, men; 68.4%, women) were white.

LeVois and Layard's (1995) analysis of the CPS-I cohort, which included a large number of CHD deaths, was limited by the lack of clarity on selection of subjects for analysis; for example, it is unclear what percent of subjects were excluded because their own smoking habits were missing or because the smoking habits of spouses were unknown. LeVois and Layard's (1995) analysis of the CPS-II cohort, after adjusting for age and race, found no association between any ETS exposure from spouses and risk of CHD mortality in men or in women; however, the emphasis of LeVois and Layard on 'any' (*i.e.*, current and former) ETS exposure from spouses and exposure from spouses who were former smokers strongly biased the results toward the null. In both men and women, there was some increase in risk when amount smoked by spouses was considered. Almost all the risk ratios (RRs) associated with each exposure category (based on amount currently smoked by spouses) were above 1.0 for women in both CPS I and CPS II and for men in CPS II. In fact, in the CPS II analysis, five of the six RRs associated with varying amounts smoked by spouses were above 1.13. These RRs by amounts currently smoked by spouses suggest that the RR for any exposure to current smokers is above 1.0 (RRs associated with any current smoke exposure were not presented and could not be computed on the basis of the data presented). As pointed out by Steenland *et al.* (1996) and Glantz and Parmley (1996), ETS exposure may have both acute and chronic effects on the heart. The effect of exposure from former smokers may be negligible, similar to the rapid reduction in heart disease risk seen among active smokers upon cessation of smoking.

The study by Steenland *et al.* (1996) presents results from four analyses of the CPS-II cohort, three of which dealt specifically with ETS exposure from spouses; the fourth analysis investigated the effects of ETS exposure at home, at work, and in other settings. The first analysis was conducted only among those married individuals with spouses also enrolled in the CPS-II study, and for whom there were valid dates of marriage and sufficient data on smoking cessation to indicate whether the spouses had smoked during marriage. The second, third and fourth analyses utilized specified subsets of eligible

subjects derived from the first analysis. Small increased risks for CHD mortality in men and women in association with current exposure to spouses' smoking were found in each of the analyses, with statistically significant results only in nonsmoking men. There was, however, no association between risk of CHD mortality in nonsmoking men and women and being married to spouses who were former smokers. The fourth analysis found small elevated risks associated with all sources of ETS exposure, although only the association between CHD risk in nonsmoking men and ETS exposure at home was statistically significant.

The differences in Steenland *et al.*'s (1996) findings and those reported by LeVois and Layard (1995) are noteworthy given that both analyses utilized data from the CPS II study. The size of the relevant study population and the number of CHD deaths included by Steenland *et al.* (1996) differed from those included by LeVois and Layard (1995). In contrast to the detailed description of the inclusion and exclusion criteria presented by Steenland *et al.* (1996), LeVois and Layard (1995) provided few details regarding their study methods. Differences in the follow-up period, in the definition of spousal smoking or other criteria for inclusion and exclusion may have contributed to the differences in these two reports.

4. Comment Summary: "OEHHA misinterprets the effects of confounding." Refers to table 6 in comments submitted by Layard and LeVois, and states that "...ETS/CHD relative risks in individual studies go both up and down after adjustment; there is no clear pattern; the adjustments are not statistically significant; nor are the adjusted ETS/CHD relative risks statistically significant. In short, it is not possible to rule out confounding as an important factor in the ETS/CHD studies."

Response: The issues of bias and confounding, and the effect of adjustment of risk estimates, were previously raised and considered (see Appendix A). The risk estimates summarized in Table 6 of the comments submitted by Layard and LeVois demonstrate our previous response, that estimates of risk were almost always strengthened by adjustment. Of the seven studies listed in the table, all of the risk estimates increase with adjustment, with the exception of the two studies by He (1989 and 1994) and one gender group in the study by Dobson in which the change is very small (from 1.04 to 0.97 after adjustment).

5. Comment Summary: "OEHHA has failed to demonstrate that an ETS/CHD causal association is biologically plausible." The draft "attempts to rely upon irrelevant animal studies, mechanistic conjectures and the implausible and unproven hypothesis that ETS poses a greater risk than active smoking on a per unit basis." The draft ignores a report by the CRS [Congressional Research Service] which questions the biological plausibility of ETS/CHD "because such estimates are much greater than would be predicted from the relatively small amount of nicotine and carbon monoxide in ETS, and approach the CHD risk estimated for actual smoking", as well as a report by Dr. Gori.

Response: The issues of the relevance of the data on mechanism of action and animal studies, and the risk of ETS exposure compared to that of active smoking (including those raised by Dr. Gori), have been previously raised and considered (see Appendix A, pages A-43 to A-48). The report of the CRS, titled *Environmental Tobacco Smoke and Lung Cancer Risk*, briefly discusses some of the issues regarding cardiovascular effects (in three pages in an appendix), and states, “A full analysis of these issues [heart disease in adults and respiratory illness in children] is beyond the scope of this paper...” The question of whether the magnitude of the effect of ETS on CHD is consistent with the active smoking relationship with CHD is discussed in the draft (pages 8-25 to 8-26). The draft indicates that an increased risk of about 30% for ETS exposure and CHD estimated from the available studies is believable relative to the two- to three-fold risk seen in more recent studies of active smokers. While these relative risks are considerably higher than those estimated from earlier studies of active smokers, the higher risks for CHD in more recent cohorts may be due to the earlier age of smoking initiation, deeper inhalation during smoking, and other differences in smoking behavior. Moreover, the risk estimates for studies of active smoking and heart disease use as a comparison group all nonsmokers, which includes those with and without exposures to ETS. Because the risk estimates in active smoking and ETS studies use different baseline comparison groups, the numerical values are not directly comparable.

6. Comment Summary: “OEHHA’s attributable risk calculations for CHD morbidity and mortality are unwarranted.” They are “based on the false premise that a causal association has been established between ETS exposure and CHD.” The calculations are “simplistic and fundamentally flawed”, “based on outdated and widely discredited analyses”, “fail to take into account important and large new studies, such as Layard/LeVois (1995)”, “vastly overestimate ETS exposure in California and essentially ignore wide variations in reported results and fundamental weaknesses in the underlying epidemiologic studies.”

Response: As addressed above in comments 1, 2, 3, and 5, the available body of evidence does support a causal association between ETS exposure and CHD, as summarized in the draft. Issues regarding attributable risk in general were raised by several commenters; these are addressed in responses to comments on Chapter 1. The analyses which serve as the basis for the estimated annual morbidity and mortality in nonsmokers associated with ETS exposure (Table 1.1) for cardiovascular effects are quantitative reviews of the literature done by Wells (1994), Glantz and Parmley (1991), Steenland (1992), and Wells (1988). As reviewed in the draft, the conclusions of the reviews by Glantz and Parmley and Steenland were endorsed by the American Heart Association, but criticized by others who questioned, among other issues, the meaningfulness of relative risk estimates that were less than three, the authors' method of deriving the pooled risk estimate, and the inclusion of 'positive' findings that were not statistically significant. Glantz and Parmley discounted these criticisms in their responses. These and other criticisms, such as the plausibility of the magnitude of effect observed between CHD and passive smoking given assertions that the association with

active smoking is relatively weak, mirror the issues raised in the above comments regarding the evidence for a causal association.

Gio B. Gori, The Health Policy Center, for The Tobacco Institute

1. Comment Summary: The draft “is largely based not on a genuine weight of evidence analysis of extant reports, but rather on selective and conjectural arguments advanced by other reviews.”

Response: To provide background for the reader, previous reviews of ETS and CHD are summarized briefly in Section 8.02. As described in response to comment 1 under The Tobacco Institute, a weight of evidence approach was used to describe the body of evidence, and the draft describes in detail the basis for the finding of a causal association of ETS exposure and risk of CHD, in terms of the findings of the published reports.

2. Comment Summary: “CHD risk values in the vicinity of 1.3 for ETS exposures, while acknowledging that CHD risks associated with active smoking average 1.7” as estimated by other reviewers “must stand as testimony to the presence of common risk factors that ETS studies were obviously unable to identify and account for.”

Response: The question of whether the magnitude of the effect of ETS on CHD is consistent with the active smoking relationship with CHD is discussed in the draft (pages 8-25 to 8-26). Briefly, the relative risks for CHD in relation to light smoking reported in recent studies are considerably higher than the risk estimates reported in studies conducted in 1950-1960; earlier cohort studies generally reported relative risks of 1.2 to 1.6 for men smoking 1-9 cigarettes/day compared to nonsmokers, while in more recent studies, relative risks of 2 to 3 were reported for women and men who were light smokers (1-4 or 5-14 cigarettes/day) compared to nonsmokers. The higher relative risks for CHD in more recent cohorts may be due to the earlier age of smoking initiation or deeper inhalation during smoking. The two to three fold risk between active smoking and CHD in contemporaneous studies suggest that the increased risk of about 30 percent for ETS exposure and CHD is believable. There is some suggestion that the association between active smoking and CHD may be stronger in younger subjects than in older subjects, which suggests that age-specific effects, and cohort effects of ETS exposure on risk of heart disease should be monitored in future studies.

3. Comment summary: The commenter compares the findings of the analyses conducted by LeVois and Layard (1995) and Layard (1995) of the CPS data and the NMFS data, respectively, with the analysis by Steenland *et al.* of the CPS data.

Response: Issues related to a comparison of these studies are addressed in the response comment 3 of the The Tobacco Institute, above.

4. Comment summary: The commenter presents a chart of results of published studies, noting that “the right-skewed funnel shape of the graph should be interpreted as evidence of publication bias [of positive results]...” Large studies (such as the Framingham study and others) “report a no effect threshold for CHD at the active smoking of 10 or fewer

daily cigarettes” which “negates the credibility of ETS epidemiologic studies”, whose results are due to “undetected confounders”.

Response: The issues of publication bias, issues in interpretation of the results of the Framingham study, and confounding in studies of ETS and CHD. These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.

5. Comment Summary: With regard to mechanistic data, the draft “has completely ignored [the commenter’s] published review that documents the implausibility of significant ETS effects” on the endpoints discussed in the document as relevant to the mechanism of action of ETS on CHD. The same review “documents the irrelevancy of animal studies to the evaluation of possible CHD risk from ETS in humans”, and the commenter suggests that such reports “do not verify or support” a causal association of ETS exposure with increased CHD risk.

Response: The issues of the relevance of the data on mechanism of action and animal studies, and the risk of ETS exposure compared to that of active smoking (including those raised by Dr. Gori). These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.(see Appendix A, pages A-43 to A-48).

Maurice LeVois and Maxwell Layard, Environmental Health Resources, for The Tobacco Institute

1. Comment Summary: “It is incorrect ... that recent ETS/CHD data support the claim that ETS increases the risk of heart disease.” Comparing their analyses of CPS II data (LeVois and Layard, 1995) with those of Steenland *et al.*(1996), the commenters focus on differences in exclusion of subjects, exposure definitions and adjustment for confounders, and find that “the results of their [Steenland *et al.*] analysis of CPS-II data are essentially in agreement with ours...” The commenters state that, in drawing conclusions the draft ignores their “very large null” study.

Response: All the available studies were reviewed and considered as part of the weight of evidence approach (described in Section 1.4) (see the response to comments 1 and 2 of The Tobacco Institute). Issues related to a comparison of the studies of concern to the commenters are addressed in the response to comment 3 of The Tobacco Institute, as are methodologic limitations of the study conducted by LeVois and Layard (1995).

2. Comment Summary: The commenters raise concerns about publication bias in the epidemiologic literature as well as conclusions regarding workplace ETS exposure and CHD risk.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.(see page A-47).

3. Comment summary: According to the commenters, “...that the ETS/CHD risk is ‘strengthened by adjustment’ ...implies that a protective effect is removed by adjustment for other CHD risk factors... This is implausible...” The commenters state that “the claim that adjustment for confounders strengthens most ETS/CHD associations is false,” and presents a table summarizing results from other CHD studies.

Response: The risk estimates summarized in table 6 of the submitted comments are addressed above (comment 4 of The Tobacco Institute); the issues of bias and confounding, and the effect of adjustment of risk estimates, were previously raised and considered (see Appendix A). The idea put forward by the commenters, that a protective effect is removed by adjustment for other CHD risk factors, is not the standard interpretation of adjustment for confounding and is not proposed by the draft.

4. Comment summary: The reviews cited in the draft as supportive of the OEHHHA assessment “add nothing new in terms of data, and their conclusions were based upon a selective use of the available data.”

Response: Previous reviews of ETS and CHD (summarized briefly in Section 8.02) as reviews are not intended to add data but rather to synthesize the available data. These reviews are presented as background for the reader. The draft provides an independent review of each of the available studies, and discusses the basis for the finding of a causal association of ETS exposure and risk of CHD in terms of the findings of these studies.

5. Comment summary: The draft’s criticism of the exposure definition “misrepresents the data presented in the [LeVois and Layard] report... Reporting ‘any’ ETS exposure is consistent...with a test of the publication bias hypothesis that was the focus of the analysis.”

Response: LeVois and Layard (1995) examined the effect of ‘any’ ETS exposure, combining those who had currently smoking spouses and those who had exposure from spouses who were former smokers. They also reported results for exposure based on amount smoked by current spouses, and as mentioned above (response to comment 3 of The Tobacco Institute), and, in both men and women there was some increase in risk when amount currently smoked by spouses was considered. But they did not report results for any ETS exposure from current smoking spouses, that is, all those exposed currently to whatever amount of smoking. The finding these investigators emphasized was the reduction in risk among men married to exsmokers when results from the two CPS studies were combined. As the commenters suggest, this emphasis is consistent with their hypothesis of publication bias; such an approach does not, however, provide useful information with regard to the CHD risk associated with current exposure to ETS.

6. Comment Summary: Regarding the draft’s critique of the Layard (1995) report, the commenters object to statements regarding the absence of a listing of causes of death among controls and the possible association of these with exposure to tobacco smoke, the

age adjustment used, including the age groups, and the description of results for males ages 25 to 44.

Response: In the Layard (1995) study, controls were selected from the same study population as cases, with exclusions based on a list of specified causes of death considered by the author to be smoking related. However, the actual causes of death among controls were not presented, making it impossible for the reviewer to assess the extent to which the distribution of causes of death in controls may have contributed to the null result found in this study. Not all causes of death considered to be related to tobacco smoke exposure (e.g., asthma) were on the list of exclusions used by the author.

With respect to age adjustment and reported results for males ages 25 to 44, several concerns exist. First, it appears that the controls were not matched to cases on age at death, as discussed above (response to comment 3 of The Tobacco Institute). Secondly, the study was supposed to include all deaths among males aged 25-44 years but the mean ages of male cases were considerably older (cases, 72.6 years; controls, 64.8 years). The reason for this discrepancy was not explained in the paper; the commenters state that “The NMFS included about 1% of deaths from CHD...at ALL ages. The inclusion of all CHD deaths in the above ‘young’ [25-44 males] age groups was IN ADDITION to the 1%.”[emphasis in original]. Why all male CHD deaths would be grouped in the category of 25-44 year olds, as this statement seems to indicate, raises more questions than it answers.

7. Comment summary: Regarding responses (in Appendix A) to previous comments submitted by LeVois, comments made in the previous submission are repeated, and reasons are presented as to why the response to these is found to be inadequate.

Response: These issues have been raised, considered and addressed in the previous comment period or elsewhere within this set of comments/responses.. We regret the commenters found our responses inadequate.

RJ Reynolds

RJ Reynolds, submitted by Mary Ward, attorney

1. Comment Summary: In reference to the above comments by Carr and DeLuca, the use of medical records, death certificates and interviews is less accurate than use of autopsy data in diagnosing cardiovascular effects. These inaccuracies are more likely to occur in patients who are married to smokers, therefore introducing variability and uncertainty in the results.

Response: This statement is a claim that lacks substantiation. The hypothetical misdiagnosis biases presented by the commentator neither discredit the methods

employed in the 17 studies, nor provide any basis to conclude that ETS-exposed individuals would be selectively favored in cases of misdiagnosis.

2. Comment Summary: Use of death certificates to calculate incidence of particular diseases has many potential problems, as indicated by Moriyama (1966) (summarized by Feinstein, 1985). Use of autopsy studies would eliminate much of the uncertainty in diagnosis of CHD.

Response: Extensive numbers of autopsy studies on ETS and CHD are not available. Although this method might eliminate some areas of uncertainty in characterizing the exact cause of death, the studies in the ETS document employed commonly used methodologies that were scientifically peer-reviewed.

3. Comment Summary: Approximately one third of myocardial infarctions remain undetected (Sigurdsson *et al.*, 1995; O'Sullivan, 1996). This leads to selection bias if only living subjects are studied.

Response: This would only be true if those suffering the more severe infarctions were exposed to appreciable levels of ETS, which has not been determined. The ETS document considered both living and deceased subjects.

4. Comment Summary: As much as 50% of sudden unexpected cardiac deaths in men and 64% of sudden cardiac deaths in women occur without prior symptoms of coronary artery disease (the Framingham study, Kannel and Schatzkin, 1985).

Response: Comment noted.

5. Comment Summary: Therefore, a majority of the first time heart attack patients in the overall United States population do not have medical records indicating coronary artery disease, with the percentage for women being higher.

Response: Comment noted.

6. Comment Summary: If a patient is admitted to the hospital and dies prior to a diagnostic evaluation, the treating physician frequently assumes that the patient died from a heart attack (Goldacre, 1993).

Response: Comment noted.

7. Comment Summary: A significant percentage of other fatal acute medical conditions are often incorrectly certified, e.g., pulmonary embolism (Morgenthaler and Ryu, 1995), stroke (Reggio *et al.*, 1995; Devine *et al.*, 1996) and asthma (Model, 1995; Guite and Burney, 1996).

Response: Comment noted.

8. Comment Summary: An autopsy is the only method that can accurately establish a cause of death. Even patients who have medical records detailing pre-existing conditions frequently die from causes unrelated to their pre-existing condition (Goldacre, 1993).

Response: This comment is overstated. An autopsy may yield a greater precision in the determination of cause of death in certain cases. Other methods are also accurate.

9. Comment Summary: The autopsy rate in the United States is extremely low in university hospitals (8%) and many community hospitals perform no autopsies (Hutchins, 1997).

Response: Comment noted.

10. Comment Summary: Of the seventeen epidemiologic studies of ETS exposure and cardiovascular disease, only one study (Svendsen *et al.*, 1987) used autopsies to certify the diagnosis of cardiovascular disease, and even Svendsen used only a small number of autopsy results.

Response: Many of the studies in the document examined not only death, but symptoms associated with CHD, such as abnormal electrocardiograms and angina.

11. Comment Summary: The dependency of the epidemiologic studies conducted to date on inadequate measures of cardiovascular disease incidence (death certificates, medical records, patient and surrogate interviews) places a large variability upon and creates significant uncertainty in the measurement of the “response” hypothesized to result from exposure to ETS.

Response: We do not consider the clinical measures of cardiovascular disease, or the use of medical records or patient interviews to be inadequate. The degree of uncertainty and variability in diagnoses hypothesized by the commentator is not likely to be of a serious magnitude, the uncertainties are not expected to present unidirectional bias, nor are there any viable alternatives to the measures used, since autopsy data are not widely available.

12. Comment Summary: Socioeconomic factors particularly tend to increase the tendency toward the artifactual certification of coronary artery disease in the spouses of smokers.

Response: This statement is a claim that lacks substantiation. No data or references are provided for evaluation.

13. Comment Summary: The epidemiology studies of ETS and cardiovascular disease likely suffer from a diagnostic bias that tends to overestimate the CVD risk in the nonsmoking spouses of smokers.

Response: This statement is a claim that lacks substantiation. The hypothetical misdiagnosis biases presented by the commentator neither discredit the methods employed in the 17 studies, nor provide any basis to conclude that ETS-exposed individuals would be selectively favored in cases of misdiagnosis.

Others

Gordon Fung, American Heart Association

Dr. Fung submitted a review of the draft conducted at their request by Dr. Neal Benowitz of the University of California at San Francisco. The following are comments made by Dr. Benowitz.

1. Comment Summary: The epidemiological data seem convincing that ETS increases the risk of CHD by about 30% in nonsmokers.

Response: Comment noted.

2. Comment Summary: The biological plausibility section summarizes the available data, but is not fully convincing. The observational data on carotid wall thickness are the cleanest data. The data on impaired arterial endothelial function in passive smokers is a little hard to understand. The data in active smoking suggests that nitric oxide is destroyed by exposure to oxidant gases. It is not likely that the oxidant gas exposure is very great in passive smoking, because oxidant gases are highly reactive and would have dissipated in the environment before being taken in by the passive smoker.

Response: OEHHA does not disagree with the commenter that oxidant gas exposure is unlikely to be causing the vascular effects seen in passive smokers. The discussion has been modified to indicate that “The activity or production of endothelial nitric acid may be impaired...” to clarify this point.

3. Comment Summary: Data on impaired exercise tolerance are based on studies of individuals exposed to extremely high concentrations of ETS while exercising. The relevance of this test procedure to individuals working at usual levels of ETS is unclear. The absorption of carbon monoxide will reduce oxygen-carrying capacity and in theory could contribute to adverse effects of ETS. However, in most studies where carbon monoxide levels have been measured, there is no difference in individuals who are or are not exposed to ETS. Likewise, absorption from nicotine, which is suggested as a mechanism for adverse cardiovascular effects, is very low in passive smokers, such that nicotine is unlikely to have any hemodynamic effects.

Response: Some data regarding carboxyhemoglobin levels in ETS-exposed individuals has been included in the document (Aronow, 1978) and its potential to contribute to adverse cardiovascular effects has been suggested. The issue of exposure to nicotine

from ETS has been addressed in Section 2.3.5 Indoor Air Concentrations of Nicotine which notes that indoor environments in the US show a nicotine concentration range from 0.3 to 30 µg/m³. However, we take the point that the corresponding levels within the ETS exposed may not be sufficiently high to cause significant effect.

4. Comment Summary: Endothelial cell damage has been reported in ETS-exposed individuals, but is unlikely to be explained by nicotine, because of extremely low levels as noted above. One intriguing possibility is that ETS exposure produces chronic inflammation in the lungs, which itself may have promoting effects on atherosclerosis. Chronic inflammation could perhaps also explain the high fibrinogen levels that are reported in ETS-exposed nonsmokers.

Response: The language in the document regarding nicotine and carbon monoxide as the cause of changes in endothelial cells and platelet aggregate ratios has been modified to reflect the commenter's concern regarding the likelihood of involvement of these compounds. While intriguing, the potential role of chronic inflammation as a contributor to high fibrinogen levels remains speculative at this point.

Stanley M. Greenfield

1. Comment Summary: Several analyses in the Steenland *et al.* (1996) paper find decreases in relative risks of CHD for increased ETS exposures. Analysis 1 shows the risk for males decreases with increased spousal exposure in cigarettes per day: only the overall result and that for the subgroup with lowest exposure is statistically significant. For females the risk decreases from 1.15 at <20 cigarettes/day to 0.99 at 21-39, increasing to 1.04 for 40+ cigarettes/day (none of these results being statistically significant). Analysis 3 shows similarly contradictory results. This is not explained in the report. The failure to note the downward trends is an example of biased reporting.

Response: None of the trends claimed to exist in the results reported (Table 8.1) are statistically significant. With the exception of female never smokers with a spouse smoking 21-39 cigarettes/day (OR = 0.99), and male spouses of former smokers (OR = 0.96), odds ratios calculated in analysis 1 are in excess of 1.0, although in this analysis only the findings for all males (OR = 1.22, 95% CI = 1.07 - 1.40) and males whose spouse smokes < 20 cigarettes/day (OR = 1.33, 95% CI = 1.09 - 1.61) are statistically significant. For both males and females, the upper confidence limits for the low points in the dose-response relationship include the best estimate (and for males the upper 95% confidence limit also) of the overall value. It is hard to argue for a credible trend of effect with dose in either direction in the face of these data, as OEHHA's summary noted in the report. The appearance of an inverse trend of response with exposure is only achieved by ignoring the control values, and in one case the high-dose value also. Similar results are obtained by Analysis 3. By contrast, using Analysis 2, all the odds ratios for exposed males (apart from spouses of former smokers) are in excess of 1.0, each increment in estimated exposure is matched by a positive increment in OR, and that for males whose spouse smoked 30+ cigarettes/day is significantly elevated (OR = 1.25, 95% CI = 1.01 -

1.53). The assertion of a possible trend (of increasing response with dose) is clearly more reasonable in this case. In the case of the female subjects, in this analysis the low exposure group has an OR noticeably (but not significantly) below 1.0, but the OR increases steadily from this low point. OEHHA does not, however assert that such a trend is present in either case, but merely alerts the reader to the possibility of its existence. Since the alleged negative trends are supported neither by the underlying data, nor by any reasonable inferences from other sources, OEHHA did not find any occasion to comment on them in the report.

2. Comment Summary: “The ... Steenland *et al.* (1996) study ... clearly demonstrates the ETS effect is greater on males than on females. ... The OEHHA report does not address this gender differential”.

Response: Although the odds ratios reported for male spouses of all current smokers are larger than the corresponding figures for females, these differences are not statistically significant, and individual exposure groups do not all show this relationship. Even if this differential is considered to be apparent in this particular study, this does not necessarily show that “the ETS effect is greater on males than on females” - a number of possible explanations could be advanced which do not assume a differential health impact of ETS. Several other studies do not show a similar effect; indeed some comments have proposed an opposite conclusion. Since OEHHA did not see compelling evidence of an important effect in this study, this possibility was not remarked on in the report.

Otto J. Mueksch

1. Comment Summary: Dr. Glantz and another associate seem to be the only ones coming up with figures for coronary heart disease. Even the EPA did not buy their theory. And to quote from the special report from Consumer Research: “None of the ETS epidemiological studies is a high validity randomized prospective intervention study designed to evaluate whether or not a reduction in the level of exposure is associated with a reduction in risk of cardiovascular disease. None of the studies on ETS and cardiovascular disease measured or in any way directly quantified actual exposure to ETS.”

Response: Many of the studies presented in the document show significantly increased risks for CHD with ETS exposure. The 1992 Consumer Research article considers 9 of the 17 epidemiological studies included in the ETS document. The article urges caution in interpretation of the data available at the time. Since that time, in addition to the 8 studies not discussed in the Consumer Research report, a host of supporting evidence of the biological role of ETS in CHD etiology (described in Section 8.3 of the ETS document) has been collected.

Marty Ronhovdee

1. Comment Summary: The list of critics of the review by Glantz and Parmley should include the U.S. EPA, who still has not endorsed the report. The Congressional Research Service concluded in 1994 that the Glantz figures seemed “implausible”.

Response: The report of the CRS, titled *Environmental Tobacco Smoke and Lung Cancer Risk*, briefly discusses some of the issues regarding cardiovascular effects (in three pages in an appendix), and states, “A full analysis of these issues [heart disease in adults and respiratory illness in children] is beyond the scope of this paper...” The question of whether the magnitude of the effect of ETS on CHD is consistent with the active smoking relationship with CHD is discussed in the draft (pages 8-25 to 8-26). The draft indicates that an increased risk of about 30% for ETS exposure and CHD estimated from the available studies is believable relative to the two- to three-fold risk seen in more recent studies of active smokers. While these relative risks are considerably higher than those estimated from earlier studies of active smokers, the higher risks for CHD in more recent cohorts may be due to the earlier age of smoking initiation, deeper inhalation during smoking, and other differences in smoking behavior. Moreover, the risk estimates for studies of active smoking and heart disease use as a comparison group all nonsmokers, which includes those with and without exposures to ETS. Because the risk estimates in active smoking and ETS studies use different baseline comparison groups, the numerical values are not directly comparable.

Jay R. Schrand

1. Comment Summary: The commentator notes that individuals prone to sleep apnea are at higher risk for hypertension, coronary heart disease, and stroke, and contends that much of the deleterious results of tobacco use are actually the result of pre-existing illnesses such as sleep apnea, “that are being partially treated by nicotine.” The commentator also has concerns regarding the potential for the phenomenon of assortive mating to confound epidemiological studies of ETS.

Response: The issues of sleep apnea (and a genetic predisposition to it) and assortive mating as confounders in establishing the effects of ETS have been considered in another portion of the comments/responses.

Carol Thompson, Smokers’ Rights Action Group

1. Comment Summary: The commentator rejects the conclusion that either active or passive smoking have a causal role in cardiovascular disease, proposing instead that all the observed effects are instead due to infection by “*Helicobacter pylori*, *Chlamydia pneumoniae* and no doubt other pathogens yet to be discovered”.

Response: OEHHA is aware of the cited reports of the role of infectious agents in cardiovascular disease, but does not find the commentator’s argument convincing.

2. Comment Summary: The commentator proposes a conspiracy theory to explain the numerous efforts by public health agencies to educate the public about the dangers of both active and passive smoking.

Response: This does not appear to be a scientific argument, and is therefore outside the scope of the current process.

Judson Wells

1. Comment Summary: The paper, cited by Wells (1994) covering the same data as Sandler *et al.* (1989) is Helsing *et al.* (1988), not Svendsen *et al.* (1987).

Response: Correction noted. The comparison of the two papers on this data set, and the discussion of the Svendsen *et al.* (1987) study (pp. 8-5 and 8-7 of the final draft), cite the sources correctly.

2. Comment Summary: The Kawachi *et al.* study is now in press: *Circulation* (1997)

Response: OEHHA thanks Dr. Wells for this additional information. The study has been added to those summarized in the document.

3. Comment Summary: There is a new study: Ciruzzi *et al.* (1996). Abstract: Passive smoking and the risk of acute myocardial infarction. Presented at the XVIIIth Congress of the European Society of Cardiology, August 25-29, 1996. *Eur Heart J* **17**(Abstract supplement):309. This is a large study (336 cases) from Argentina. The authors report substantial heart disease risks from ETS.

Response: OEHHA thanks Dr. Wells for this additional information, and notes that the conclusions in this abstract are in line with the overall weight of evidence described in the report. OEHHA retains an interest in ongoing research into health effects of ETS, and looks forward to the appearance of a full report on this new study.

4. Comment Summary: Lee's criticism of Hirayama (1984) is discussed, but does not refer to Hirayama's reply.

Response: The final draft document cites Hirayama (1990) in the discussion of the study and of the criticisms made by Lee (1990).

5. Comment Summary: According to one of the authors (Dr. Sandler), the reason for the discrepancy in results between the reports by Helsing *et al.* (1988) and Sandler *et al.* (1989) is that different analytical methods were used: the methods were about as good as each other, and since the same basic data were used, the two estimates of relative risk are equally valid.

Response: OEHHA thanks Drs. Wells and Sandler for this additional information (It is also noted that the two risk estimates, although different, include overlapping confidence intervals, and these intervals exclude $RR = 1.0$)

6. Comment Summary: Page 8-13, paragraph 3, line 4 (discussion of LeVois and Layard): “First, results ... to current smoker by excluding ...” should read “including”.

Response: Correction noted.